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## **A cognitive-neurophysiological investigation of ADHD, associated disorders and risk or protective factors**

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# **A cognitive-neurophysiological investigation of ADHD, associated disorders and risk or protective factors**

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## Abstract

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This thesis uses a combination of cognitive-neurophysiological and genetically-sensitive longitudinal designs to study the associations of attention-deficit/hyperactivity disorder (ADHD) with bipolar disorder (BD) and preterm birth, as well as with the risk or protective factors IQ and physical activity. Previous research on preterm-born individuals and individuals with BD suggests ADHD-like symptoms and cognitive impairments, but direct comparisons are limited. Here, we first examine how cortical activity patterns differ between women with adult ADHD and women with BD during rest and task conditions to identify impairments that are specific to or shared between the disorders. The findings provide evidence for commonalities in brain dysfunction between ADHD and BD: frontal theta power may play a role as a marker of neurobiological processes in both disorders. Second, we investigate whether the ADHD-like symptoms and cognitive-neurophysiological impairments seen in preterm-born adolescents are identical to those in ADHD by directly comparing ADHD symptom scores and performance on a cognitive-neurophysiological test battery sensitive to impairments in ADHD across preterm-born adolescents, term-born adolescents with ADHD and term-born controls. We find that ADHD symptoms are increased in the preterm group compared to controls. The analyses further indicate similarities in brain function between ADHD and preterm birth, as well as unique impairments in the preterm group. Taken together, these results suggest that preterm birth may present a risk factor for both ADHD and additional impairments. Third, using twin data we carry out a developmental-genetic analysis of the association between ADHD and IQ, showing that ADHD symptoms and IQ scores significantly predict each other over time. Finally, we explore a putative protective factor for ADHD by investigating the effect of physical activity on ADHD symptoms. Using a population-based sample of twins, we show that physical activity is inversely associated with ADHD symptoms, even after adjusting for unmeasured confounding. Overall, we demonstrate certain commonalities in brain dysfunction between ADHD and BD. Whereas preterm birth and lower IQ present risk factors for ADHD, physical activity emerges as a potential protective factor.

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## Statement of authorship

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The research described in this thesis was undertaken using both primary and secondary data from a number of studies. I am grateful to the primary investigators for providing me with access to these datasets and to the participating families and individuals.

The results reported in chapter 2 are based on data from the Female Experiences and Brain Activity (FEBA) Project, which compared adult women with ADHD, bipolar disorder and control participants (N=60) on a range of clinical, cognitive and neurophysiological measures. FEBA, led by Prof Jonna Kuntsi, was supported by an Economics and Social Research Council (ESRC) studentship awarded to Glenn Kitsune (ES/100971X/1) and part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre and Dementia Unit at South London and Maudsley NHS Foundation Trust and King's College London.

The results reported in chapter 3 and 4 are based on data from the Study of Preterm birth and Inattention (SPIN), which assessed preterm-born adolescents and their siblings, and on data from a follow-up project (Sibling EEG Follow-up Study; SEFOS) of a clinically ascertained ADHD-proband and control sibling-pair sample. SPIN, led by Prof Jonna Kuntsi, was supported generously by Action Medical Research (GN2080). SEFOS, also led by Prof Jonna Kuntsi, was funded by grants from Action Medical Research and the Peter Sowerby Charitable Foundation (GN1777).

The results reported in chapter 5 are based on data from the Twins Early Development Study (TEDS), led by Prof Robert Plomin and supported by a programme grant (G0901245; and previously G0500079) from the UK Medical Research Council (MRC) and by grants (HD044454 and HD059215) from the US National Institutes of Health (NIH).

The results reported in chapter 6 are based on data from the Swedish Twin Study of CHild and Adolescent Development (TCHAD), led by Prof Paul Lichtenstein and supported by funding from the Swedish Research Council for

Health, Working Life and Welfare Project (2012-1678), the Swedish Research Council (2011-2492; 2014-3831), and The Swedish Foundation for International Cooperation in Research and Higher Education (STINT; IG2012-5056).

The present thesis represents my own work. For chapter 2, I formulated the research questions under the guidance of Dr Glenn Kitsune and supervisor Prof Jonna Kuntsi. I, further, processed data, conducted analyses and interpreted the findings under the supervision of Prof Jonna Kuntsi. For chapters 3 and 4, using data from the SEFOS and SPIN projects, I formulated research questions, analysed data, and interpreted the findings under the supervision of Prof Jonna Kuntsi and Dr Gráinne McLoughlin. For the SPIN project, collection of clinical and EEG data, as well as processing of the data, was shared between myself, research workers Hannah Sims, Rachel Sparrow and Stacey Eysers, as well as PhD students Sarah James and Giorgia Michellini. I was responsible for the formulation of a research question, conducting the model-fitting analyses and interpreting the findings for the quantitative genetics analysis in chapter 5 under the supervision of Dr Frühling Rijsdijk, Prof Jonna Kuntsi, and Prof Philip Asherson. For chapter 6, I formulated the research questions, conducted the analysis and interpreted the results under the supervision of Dr Henrik Larsson, and Prof Jonna Kuntsi.

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## Publications

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*Sections of chapter 1 are adapted from the following publication (reprinted by permission of Elsevier):*

**Rommel A-S**, Halperin JM, Mill J, Asherson P & Kuntsi J. (2013). Protection From Genetic Diathesis in Attention-Deficit/Hyperactivity Disorder: Possible Complementary Roles of Exercise. *Journal of the American Academy of Child and Adolescent Psychiatry* **52**, 9, p. 900-910.

*Chapter 2 is adapted from the following publication in preparation:*

**Rommel A-S**, Kitsune GL, Michelini G, Hosang GM, Asherson P, McLoughlin G & Kuntsi J. Commonalities in EEG spectral power abnormalities between ADHD and bipolar disorder during rest and cognitive performance.

*Chapter 5 is based on the following publication (available under the Creative Commons licence):*

**Rommel AS**, Rijdsdijk F, Greven CU, Asherson P & Kuntsi J. (2015). Longitudinal twin study of the direction of effects between ADHD symptoms and IQ. *PloS one*, **10**, 4, e0124357.

*Chapter 6 is based on the following publication (reprinted by permission of Elsevier):*

**Rommel A-S**, Lichtenstein P, Rydell M, Kuja-Halkola R, Asherson P, Kuntsi, J & Larsson H. (2015). Is Physical Activity Causally Associated With Symptoms of Attention-Deficit/ Hyperactivity Disorder? *Journal of the American Academy of Child and Adolescent Psychiatry*, **54**, 7, 565–570.

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## Table of Contents

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ABSTRACT .....	2
STATEMENT OF AUTHORSHIP .....	3
PUBLICATIONS.....	5
TABLE OF CONTENTS .....	6
LIST OF FIGURES .....	11
LIST OF TABLES.....	12
ACKNOWLEDGEMENTS .....	13
ABBREVIATIONS .....	15
CHAPTER 1. INTRODUCTION .....	18
1.1 CLINICAL SYMPTOMS AND DIAGNOSIS OF ADHD .....	19
1.1.1 Categorical vs. dimensional approach .....	21
1.1.2 Parent-, teacher- and self-report.....	22
1.1.3 Summary .....	25
1.2 EPIDEMIOLOGY .....	26
1.2.1 Gender differences .....	27
1.2.2 Co-occurring symptoms and disorders .....	28
1.2.3 Summary .....	30
1.3 TREATMENTS AND INTERVENTIONS .....	30
1.3.1 Physical activity .....	33
1.3.2 Summary .....	34
1.4 AETIOLOGY OF ADHD.....	34
1.4.1 Quantitative genetics .....	35
1.4.2 Molecular genetics.....	37
1.4.3 Environment .....	39
1.4.4 Gene-environment interplay .....	40
1.4.5 Summary .....	41
1.5 COGNITIVE AND NEUROPHYSIOLOGICAL IMPAIRMENTS IN ADHD .....	41

1.5.1 Phenotypic studies of cognitive impairments .....	42
1.5.2 Quantitative genetic studies of cognitive impairments in ADHD .....	44
1.5.3 Phenotypic studies of neurophysiological impairments in ADHD.....	46
1.5.4 Summary .....	54
1.6 BIPOLAR DISORDER.....	54
1.6.1 Clinical symptoms and epidemiology.....	55
1.6.2 Cognitive-neurophysiological impairments .....	59
1.6.3 Summary .....	63
1.7 PRETERM BIRTH .....	63
1.7.1 Epidemiology .....	63
1.7.2 Cognitive-neurophysiological impairments .....	68
1.7.3 Summary .....	72
1.8 AIMS AND OBJECTIVES .....	73
1.8.1 Chapters 2, 3 and 4 .....	73
1.8.2 Chapters 5 and 6 .....	74
CHAPTER 2. COMMONALITIES IN EEG SPECTRAL POWER ABNORMALITIES BETWEEN ADHD AND BIPOLAR DISORDER DURING REST AND COGNITIVE PERFORMANCE .....	76
2.1 ABSTRACT .....	76
2.2 INTRODUCTION .....	77
2.3 METHOD .....	80
2.3.1 Sample .....	80
2.3.2 Procedure and cognitive-performance measures .....	81
2.3.3 Electrophysiological recording and analysis .....	82
2.3.4 Statistical analysis .....	83
2.4 RESULTS .....	84
2.4.1 EEG power .....	84
2.5 DISCUSSION.....	85
CHAPTER 3. ALTERED EEG SPECTRAL POWER IN ADOLESCENTS WITH ADHD AND PRETERM BORN ADOLESCENTS DURING REST AND COGNITIVE PERFORMANCE .....	91
3.1 ABSTRACT .....	91
3.2 INTRODUCTION .....	93



3.3 METHOD .....	96
3.3.1 Sample .....	96
3.3.2 Procedure .....	100
3.3.3 Measures.....	100
3.3.4 Statistical analysis .....	103
3.4 RESULTS .....	104
3.4.1 Full sample .....	104
3.4.2 Age-matched subsample .....	107
3.5 DISCUSSION .....	108
CHAPTER 4. NEUROPHYSIOLOGICAL IMPAIRMENTS OF ATTENTION AND INHIBITION: A COMPARISON OF ADOLESCENTS WITH ADHD AND ADOLESCENTS BORN PRETERM .....	112
4.1 ABSTRACT .....	112
4.2 INTRODUCTION .....	114
4.3 METHOD .....	117
4.3.1 Sample .....	117
4.3.2 Procedure .....	121
4.3.3 Measures.....	121
4.3.4 Electrophysiological recording and analysis .....	123
4.3.5 Statistical analysis .....	124
4.4 RESULTS .....	126
4.4.1 Full sample .....	126
4.4.2 Age-matched sample.....	130
4.5 DISCUSSION .....	135
CHAPTER 5. A LONGITUDINAL TWIN STUDY OF THE DIRECTION OF EFFECTS BETWEEN ADHD SYMPTOMS AND IQ .....	140
5.1 ABSTRACT .....	141
5.2 INTRODUCTION .....	141
5.3 METHODS .....	143
5.3.1 Sample .....	143
5.3.2 Ethics statement .....	143
5.3.3 Measures.....	143

5.3.4 Statistical analysis .....	144
5.4 RESULTS .....	146
5.4.1 Phenotypic correlations .....	146
5.4.2 Genetic and environmental aetiologies.....	146
5.4.3 Phenotypic cross-lagged effects.....	151
5.5 DISCUSSION.....	152
5.6 REFERENCES .....	154
CHAPTER 6. IS PHYSICAL ACTIVITY CAUSALLY ASSOCIATED WITH SYMPTOMS OF ADHD? .....	157
6.1 ABSTRACT .....	158
6.2 INTRODUCTION .....	158
6.3 METHOD .....	159
6.3.1 Sample .....	159
6.3.2 Measures.....	160
6.3.3 Statistical analysis .....	160
6.4 RESULTS .....	160
6.5 DISCUSSION.....	161
6.6 REFERENCES .....	162
CHAPTER 7. GENERAL DISCUSSION AND CONCLUSIONS.....	164
7.1 SUMMARY OF AIMS.....	164
7.2 KEY FINDINGS.....	165
7.2.1 Commonalities in EEG spectral power abnormalities between ADHD and bipolar disorder during rest and cognitive performance .....	165
7.2.2 Altered EEG spectral power in adolescents with ADHD and preterm born adolescents during rest and cognitive performance .....	165
7.2.3 Neurophysiological impairments of attention and inhibition: a comparison of adolescents with ADHD and adolescents born preterm .....	167
7.2.4 A longitudinal twin study of the direction of effects between ADHD symptoms and IQ .....	167
7.2.5 Is Physical Activity Causally Associated With Symptoms of ADHD? .	168
7.3 WIDER IMPLICATIONS .....	169
7.3.1 Risk and protective factors .....	169

7.3.2 Overlap between ADHD and associated traits and disorders .....	171
7.3.3 Age effects.....	172
7.4 LIMITATIONS .....	173
7.4.1 Effects of medication .....	173
7.4.2 Generalisability .....	174
7.4.3 Rater effects .....	175
7.5 FUTURE DIRECTIONS .....	176
7.5.1 Replication .....	176
7.5.2 Advanced EEG analysis approaches.....	176
7.5.3 Sibling model fitting.....	177
7.5.4 Investigation of the effects of physical activity in ADHD .....	178
7.6 OVERALL CONCLUSIONS .....	178
REFERENCES .....	180
APPENDIX 1. PUBLICATION: PROTECTION FROM GENETIC DIATHESIS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: POSSIBLE COMPLEMENTARY ROLES OF EXERCISE. ....	231
APPENDIX 2. BASELINE CORRECTED ERP ANALYSIS FOR THE AGE- MATCHED SAMPLE.....	243

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## List of Figures

---

<b>Figure 1.1.</b> EEG frequency bands commonly investigated in ADHD.....	48
<b>Figure 1.2.</b> Simulated ERP waveform showing several ERP components according to the typical naming conventions.....	50
<b>Figure 2.1.</b> Mean frontal theta power across resting-state (EO) and task (CPT-OX) condition in women with adult ADHD, women with bipolar disorder (BD) and control women.....	85
<b>Figure 3.1.</b> Mean delta power across resting-state (EO) and task (CPT-OX) condition in (A) the full sample and (B) the age-matched adolescent subsample.....	106
<b>Figure 4.1.</b> (A) Grand average event-related potentials (ERPs) to Cue stimuli at the Cz electrode in the age-matched subsample, showing the CNV in the 1300-1650 ms window and (B) topographic maps. ....	132
<b>Figure 4.2.</b> (A) Grand average event-related potentials (ERPs) to Go stimuli at the Pz electrode in the age-matched subsample, showing the Go-P3 in the 250-500 ms window and (B) topographic maps. ....	133
<b>Figure 4.3.</b> (A) Grand average event-related potentials (ERPs) to NoGo stimuli at the FCz (above) and Cz (below) electrodes in the age-matched subsample, showing the NoGo-P3 in the 250-500 ms window and (B) topographic maps.....	134
<b>Figure 5.1.</b> Cross-lagged twin model.....	145
<b>Figure 5.2.</b> Cross-lagged path model of vocabulary and ADHD symptom scores .....	147
<b>Figure 5.3.</b> Cross-lagged path model of Raven's and ADHD symptom scores .....	148

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## List of Tables

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<b>Table 1.1.</b> Diagnostic items for ADHD based on DSM-IV-TR. ....	20
<b>Table 2.1.</b> Descriptive statistics. ....	81
<b>Table 3.1.</b> Descriptive statistics. ....	99
<b>Table 4.1.</b> Descriptive statistics. ....	120
<b>Table 4.2.</b> Cognitive and ERP measures from the CPT-OX .....	128
<b>Table 4.3.</b> Correlations between event-related potential (ERP) parameters and age across the ADHD, preterm and control groups of the full sample .....	129
<b>Table 5.1.</b> Phenotypic correlations between ADHD symptom and vocabulary scores .....	146
<b>Table 5.2.</b> Phenotypic correlations between ADHD symptom and Raven's Standard Progressive Matrices scores .....	146
<b>Table 5.3.</b> Proportions of the phenotypic correlations between ADHD symptoms and vocabulary scores due to genetic (A), shared environmental (C) and non-shared environmental (E) influences.....	149
<b>Table 5.4.</b> Proportions of the phenotypic correlations between ADHD symptoms and Raven's Standard Progressive Matrices scores due to genetic (A), shared environmental (C) and non-shared environmental (E) influences .....	149
<b>Table 5.5.</b> Transmission of genetic (A), shared environmental (C) and non-shared environmental (E) influences between ADHD symptoms and vocabulary scores over time.....	150
<b>Table 5.6.</b> Transmission of genetic (A), shared environmental (C) and non-shared environmental (E) influences between ADHD symptoms and Raven's Standard Progressive Matrices over time. ....	151
<b>Table 6.1.</b> Physical Activity Questionnaire Enquiring About the Intensity, Frequency, and Duration of the Participant's Leisure- Time Physical Activity.	160
<b>Table 6.2.</b> Descriptive statistics for raw (non-standardised) scores .....	161

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## Abbreviations

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Abbreviation	Meaning
5-HTT	Serotonin transporter gene
A	Additive genetic effects
ADHD	Attention-deficit/hyperactivity disorder
ADHD-C	ADHD combined-type
ADHD-HI	Predominantly hyperactive-impulsive type
ADHD-IA	Predominantly inattentive-type
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
BD	Bipolar disorder
BD-I	Bipolar I disorder
BD-II	Bipolar II disorder
BFIS	Barkley's functional impairment scale
BMI	Body mass index
C	Shared environment
CBT	Cognitive behavioural therapy
CD	Conduct disorder
CE	Commission error
CNS	Central nervous system
CNV	Contingent negative variation
CNVs	Copy number variants
CPT	Continuous performance test
D	Non-additive or dominant genetic effects
DAT1	Dopamine transporter gene
dB/oct	decibel per octave
DIVA	Diagnostic Interview for ADHD in adults
DMN	Default mode network
DNA	Deoxyribonucleic acid
DRD4	Dopamine receptor D <sub>4</sub> gene
DRD5	Dopamine receptor D <sub>5</sub> gene
DSM	Diagnostic and Statistical Manual of Mental Disorders



DZ	Dizygotic
E	Non-shared environment
EC	Eyes-closed resting-state condition
ECT	Electroconvulsive therapy
EEG	Electroencephalography
EF	Executive functioning
EO	Eyes-open resting-state condition
ERN	Error-related negativity
ERP	Event-related potentials
FFT	Fast Fourier Transform
fMRI	functional Magnetic resonance imaging
FRN	Feedback-related negativity
GA	Gestational age
GWAS	Genome-wide association studies
$h^2$	Heritability
HR	Hazard ratio
Hz	Hertz
ICA	Independent component analysis
ICD	International Classification of Diseases
IQ	Intelligence quotient
$k\Omega$	Kiloohm
MEG	Magnetoencephalography
MMN	Mismatch negativity
MTA	Multimodal treatment study of ADHD
MZ	Monozygotic
NICE	National Institute for Health and Care Excellence
ODD	Oppositional defiance disorder
OE	Omission error
OR	Odds ratio
PA	Physical activity
QEEG	Quantitative EEG
$r_A$	Genetic correlation
$r_C$	Shared environmental correlation

$r_E$	Non-shared environmental correlation
RR	Relative risk
RTV	Reaction time variability
SART	Sustained Attention to Response Task
SD	Standard deviation
TBR	Theta:beta ratio
WASI	Wechsler Abbreviated Scale of Intelligence
$\mu V$	Microvolt

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## Chapter 1. Introduction

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Attention-deficit/hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder, characterised by developmentally inappropriate and impairing levels of hyperactivity, impulsivity and/or inattention (American Psychiatric Association, 2013). This conceptualisation of ADHD, as presently defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association 2013), has evolved gradually over the centuries and still bears a notable resemblance to its origins today (Barkley & Peters, 2012; Taylor, 2011). The idea of inattentive, overactive and impulsive behaviour as a medical problem first arose in 1775 in a textbook written by Melchior Adam Weikard (Barkley & Peters, 2012). The universal and impairing qualities of these symptoms were then further outlined in eighteenth and nineteenth century accounts of the disorder (Crichton, 1798; Still, 1902).

Following these early descriptions, efforts were made to advance the key ideas of ADHD with the help of empirical evidence. This endeavour gave rise to the first mention of ADHD in the DSM-II, referring to the disorder as 'hyperactive child syndrome' (American Psychiatric Association, 1968). DSM-III brought about a paradigm shift both for child psychiatry more generally, by replacing aetiological formulations with simple description of observable behaviours, and ADHD more specifically, by placing equal emphasis on the inattentive, hyperactive and impulsive components of the disorder (American Psychiatric Association, 1980). As a consequence of recognising the heterogeneity in the behavioural manifestation of the disorder, two subtypes of ADHD – the inattentive and the hyperactive-impulsive subtype – were subsequently incorporated into the description of ADHD in the DSM-IV, yielding three subtypes of ADHD: the inattentive, the hyperactive-impulsive and the combined subtypes (American Psychiatric Association, 1994). Most recently, the DSM-5 (American Psychiatric Association, 2013) has been updated to include, among other things, appropriate diagnostic criteria for adults and frequently co-occurring disorders.

## **1.1 Clinical symptoms and diagnosis of ADHD**

The diagnostic criteria for ADHD employed in this thesis are based on the DSM-IV. The DSM-IV delineates nine inattention symptoms, six hyperactivity symptoms and three impulsivity symptoms, which are grouped into the inattentive and hyperactive-impulsive subscales of ADHD respectively (American Psychiatric Association, 2000) (see Table 1.1). DSM-IV criteria stipulate that a child is diagnosed with ADHD if he/she meets six or more symptoms on at least one of the two subscales. These symptoms have to have been present for at least six months and before the age of seven, and must occur across at least two settings (e.g. at home and at school) to a degree that is developmentally deviant and impairing. Finally, an ADHD diagnosis is made if these symptoms do not occur exclusively during the course of a pervasive developmental or psychotic disorder, and if they cannot be better explained by other psychiatric disorders. ADHD can be diagnosed as one of three subtypes: ADHD combined-type (ADHD-C) is diagnosed when at least six symptoms are present on both subscales, predominantly inattentive-type (ADHD-IA) is diagnosed when at least six inattentive symptoms are present; and predominantly hyperactive-impulsive type (ADHD-HI) is diagnosed when at least six hyperactive-impulsive symptoms are present. Based on the DSM-IV, adults can only be diagnosed with ADHD if they met diagnostic criteria for ADHD in childhood and continue to show symptoms and associated impairments of the disorder during adulthood. While much of the DSM-IV structure is retained in the most recent update of the ADHD classification in DSM-5 (American Psychiatric Association, 2013), changes have been made to more accurately characterise the experience of adults affected by ADHD.

In the DSM-5, symptoms required to meet diagnostic criteria depend on an individual's age, such that individuals aged 17 years and older must display five or more symptoms on at least one of the two ADHD subscales to receive an ADHD diagnosis, while children aged 16 years and younger continue to require six or more symptoms for an ADHD diagnosis. The age of onset has been raised from seven to 12 years of age (American Psychiatric Association, 2013).

**Table 1.1. Diagnostic items for ADHD based on DSM-IV-TR.**

Inattention	
1	Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
2	Often has difficulty sustaining attention in tasks or play activities
3	Often does not seem to listen when spoken to directly
4	Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure of comprehension)
5	Often has difficulty organizing tasks and activities
6	Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
7	Often loses things necessary for tasks or activities at school or at home (e.g. toys, pencils, books, assignments)
8	Is often easily distracted by extraneous stimuli
9	Is often forgetful in daily activities
Hyperactivity	
10	Often fidgets with hands or feet or squirms in seat
11	Often leaves seat in classroom or in other situations in which remaining seated is expected
12	Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
13	Often has difficulty playing or engaging in leisure activities quietly
14	Often talks excessively
15	Is often 'on the go' or often acts as if 'driven by a motor'
Impulsivity	
16	Often has difficulty awaiting turn in games or group situations
17	Often blurts out answers to questions before they have been completed
18	Often interrupts or intrudes on others, e.g. butts into other children's games

*Note:* Items replicated from the revised version of the DSM-IV (DSM-IV-TR; American Psychiatric Association 2000).

DSM criteria are similar, though not identical, to those of the International Classification of Diseases (ICD-10), which is a more stringent diagnostic tool (Sørensen, Mors, & Thomsen, 2005). In the ICD-10 (World Health Organization, 1992), which refers to ADHD as hyperkinetic disorder, ADHD is defined by the key features impaired attention and overactivity. Both impaired attention and overactivity are necessary for a diagnosis and are required to be present in more than one setting (e.g. at home and at school).

### ***1.1.1 Categorical vs. dimensional approach***

Diagnostic manuals such as the DSM (American Psychiatric Association, 2000, 2013) or the ICD (World Health Organization, 1992) define clinical diagnoses in a categorical system based on the description of behavioural symptoms because a decision to treat is of binary nature. However, taxometric analyses have shown that an ADHD diagnosis represents the extreme of a trait that varies continuously throughout the population rather than being qualitatively different (Frazier, Youngstrom, & Naugle, 2007; Haslam et al., 2006; Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Lubke, Hudziak, Derks, van Bijsterveldt, & Boomsma, 2009). These findings are substantiated by longitudinal neuroimaging research showing an association of cortical thinning during adolescence with the entire spectrum of ADHD symptoms and the ADHD diagnosis at its extreme end (Shaw et al., 2011). Further support for the view that ADHD represents the extreme end of a normally-distributed spectrum of symptoms comes from research that indicates that the aetiological contribution of genetic influences is the same for categorical and dimensional definitions of ADHD behaviours (Chen & Taylor, 2006; Chen et al., 2008; Larsson et al., 2012; Levy, Hay, McStephen, Wood, & Waldman, 1997). A genetic overlap between the categorical ADHD diagnosis and attention problems assessed as a continuous trait in the general population has also been demonstrated using polygenic risk scores derived from a discovery sample of individuals diagnosed with ADHD, which significantly predicted parent- and teacher-rated attention problems in independent population-based samples of children (Groen-Blokhuis et al., 2014; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014). The implications of these findings are that many genes and environmental

influences of small effect contribute to the spectrum of symptoms with no single factor being either necessary or sufficient for diagnosis.

A dimensional approach to ADHD is useful as it decreases the risk of possible selection biases associated with clinical samples (Rutter et al., 1990). Furthermore, investigating ADHD as a continuum enables the study of the subclinical expressions of ADHD symptoms. The categorical approach, on the other hand, affords ease of use, practicality in planning informed treatment and value in improving communication and consistency between clinicians as well as researchers (Mullins-Sweatt & Widiger, 2009). Consequently, both categorical and dimensional approaches to ADHD are valuable to studying the disorder and its underlying pathophysiology. This thesis employs both categorical and dimensional definitions of ADHD.

### ***1.1.2 Parent-, teacher- and self-report***

Clinical guidelines recommend that a systematic evaluation of ADHD symptoms in childhood should draw on accounts by multiple informers such as parents, teachers and the individual concerned (Taylor et al., 2004). Multiple-informant accounts are also useful to establish the pervasiveness of ADHD symptoms across settings, which is one of the criteria for a diagnosis of ADHD (American Psychiatric Association, 2013; World Health Organization, 1992). However, relatively low agreement between parent-, teacher- and self-ratings of ADHD symptoms has been reported, with correlations ranging from 0.3 to 0.5 (Achenbach & Rescorla, 2001; Goodman, 2001; Sollie, Larsson, & Mørch, 2013; Wolraich et al., 2004). Importantly, the methods employed to evaluate ADHD symptoms usually vary across the lifespan. While parents and teachers typically rate ADHD symptoms in childhood, ADHD symptoms in late adolescence and adulthood are usually self-rated (Asherson, 2005).

Twin studies have reported informer-specific heritability estimates for ADHD symptoms. While high heritability estimates are obtained from parent-rated ADHD symptom scores ( $h^2=70-80\%$ ) (Nikolas & Burt, 2010), heritability estimates based on self-ratings in adolescence (Ehringer, Rhee, Young, Corley, & Hewitt, 2006; Martin, Scourfield, & McGuffin, 2002; Merwood et al., 2013;

Young, Stallings, Corley, Krauter, & Hewitt, 2000) and adulthood (Boomsma et al., 2010; Haberstick et al., 2008; Larsson et al., 2013; Schultz, Rabi, Faraone, Kremen, & Lyons, 2006; van den Berg, Willemsen, de Geus, & Boomsma, 2006) are consistently lower ( $h^2 \leq 50\%$ ). Teacher-rated ADHD symptoms also generally yield lower ( $h^2 \leq 60\%$ ) (Kan, van Beijsterveldt, Bartels, & Boomsma, 2014; Kuntsi & Stevenson, 2000; Merwood et al., 2013; Thapar, Harrington, Ross, & McGuffin, 2000; Wood, Rijdsdijk, Saudino, Asherson, & Kuntsi, 2008) and more varied (Thapar et al., 2000; Wood et al., 2008) heritability estimates, especially when different teachers rate the behaviours of each twin from a pair (Derks, Hudziak, Van Beijsterveldt, Dolan, & Boomsma, 2006; Hartman, Rhee, Willcutt, & Pennington, 2007; Kan et al., 2014; Merwood et al., 2013; Saudino, Ronald, & Plomin, 2005). Since individuals with ADHD may lack insight into their problems (Hoza et al., 2005; Knouse, Bagwell, Barkley, & Murphy, 2005; Murphy & Schachar, 2000; Owens, Goldfine, Evangelista, Hoza, & Kaiser, 2007), self-ratings of ADHD may provide a less reliable measure of behaviour. One plausible explanation for the findings of lower heritability estimates for self-ratings is, therefore, greater measurement error resulting from less reliable ratings (Franke et al., 2012; Martin et al., 2002; Merwood et al., 2013). In classical twin modelling, measurement error is contained in the non-shared environmental component. As a result, measurement error can lead to an inflation of the non-shared environmental component and a decrease in the heritability estimates because the genetic, shared and non-shared environmental factors are statistically dependent components of the phenotypic variance (Rijdsdijk & Sham, 2002).

Different-teacher ratings have yielded similarly low heritability estimates as self-ratings (Kan et al., 2014; Merwood et al., 2013). Consequently, another explanation for the lower heritability estimates for self-ratings is the reliance on different informants for each twin in a pair when using self-ratings (i.e., each twin rates themselves), as opposed to one informant when the same parent or teacher rates both twins in a pair (Brikell, Kuja-Halkola, & Larsson, 2015). This explanation implicates rater effects, which could reflect true rater specific variance (Bartels, Boomsma, Hudziak, van Beijsterveldt, & van den Oord, 2007; Hartman et al., 2007) or rater bias (Freitag, Rohde, Lempp, & Romanos, 2010).



While parent-ratings of ADHD symptoms have yielded consistent heritability estimates (Nikolas & Burt, 2010), they often show low dizygotic (DZ) twin correlations of less than half the monozygotic (MZ) correlations (Kuntsi & Stevenson, 2000, 2001; Martin et al., 2002; Saudino et al., 2005; Thapar et al., 2000). This finding may be interpreted as reflecting dominant genetic factors, but may also represent influences from rater contrast effects. Contrast effects stem from an overestimation of the differences between twins, which generally reduce twin similarity more strongly in DZ compared to MZ twins (Rietveld, Posthuma, Dolan, & Boomsma, 2003; Wood, Buitelaar, Rijdsdijk, Asherson, & Kuntsi, 2010). In addition to low DZ correlations, contrast effects are further signified by significantly greater phenotypic variances for DZ than MZ twins, which aid the distinction between contrast effects and non-additive genetic effects. Some twin studies of ADHD have indeed identified contrast effects (Freitag et al., 2010; Rietveld et al., 2003; Stevenson et al., 2005). Undetected contrast effects have also been hypothesized to account for some of the non-additive genetic influences reported in ADHD (Wood, Buitelaar, et al., 2010). Short rating scales for ADHD symptoms (e.g. the 5-item SDQ hyperactivity scale or the 3-item Rutter A scale) may be more likely to elicit these contrast effects (Price et al., 2005). Consequently, longer rating scales may provide a more objective measure of ADHD symptoms. Furthermore, teacher-ratings may be less susceptible to contrast effects due to their relatively greater experience of same-age children to which they can compare the twins' behaviours (Hartman et al., 2007; Simonoff et al., 1998).

Both common and unique genetic influences on parent-, teacher- and self-ratings of ADHD symptoms have been reported (Derks et al., 2006; Hartman et al., 2007; Martin et al., 2002; McLoughlin, Rijdsdijk, Asherson, & Kuntsi, 2011; Merwood et al., 2013; Nadder, Rutter, Silberg, Maes, & Eaves, 2002; Thapar et al., 2000). A recent multivariate twin analysis found that the similarities among raters could largely be attributed to genetic influences (84%) and proposed that the difference between informants may either represent genuine non-shared environmental influences, gene-environment interaction or increased measurement error (Merwood et al., 2013). The implications of these findings are that a composite measure combining multiple-informant accounts creates a pervasive and highly heritable phenotype, which decreases the likelihood of

measurement error. Although it is apparent that rater effects impact heritability estimates for ADHD, the question of which rater assessment offers the most accurate heritability estimate is not resolved (Brikell et al., 2015). In childhood and adolescence, parent-reports seem to be the most reliable measure of ADHD symptoms. Not only do parent-rated ADHD symptoms demonstrate the highest and most consistent heritability estimates in childhood and adolescence (Nikolas & Burt, 2010), the predictive validity of parent-report with regards to long-term outcome is also more accurate than that of childhood self-report (Barkley, Fischer, Smallish, & Fletcher, 2002). For the assessment of adult ADHD, cross-informant ratings (i.e. parent- and self-ratings or clinician-, close relation- and self-ratings) have been recommended since heritability estimates and twin correlations from cross-informant studies of ADHD in adults have been in line with findings from childhood twin studies using same parent-/teacher-ratings (Brikell et al., 2015; Chang, Lichtenstein, Asherson, & Larsson, 2013; Larsson et al., 2013). However, considering cross-informant ratings for adults with ADHD may not always be feasible. The idea that lower heritability estimates for self-ratings of adult ADHD stem from the reliance on different informants for each twin in a pair (i.e., each twin rates themselves), rather than from a less reliable measure of behaviour (Brikell et al., 2015), may suggest that basing adult ADHD symptoms on self-ratings is viable.

The ADHD sample in chapter 2 was obtained from an adult ADHD clinic where ADHD diagnosis was established by a clinician based on self-report. For consistency between samples (Cheung et al., 2015a; Cheung, Rijdsdijk, McLoughlin, Asherson, & Kuntsi, 2015b; Kuntsi et al., 2015), diagnostic status in chapters 3 and 4 of this thesis was based on ADHD symptoms reported by one parent during a structured clinical interview. In chapters 5 and 6, ADHD symptoms were established using parent-ratings of DSM-IV ADHD symptoms.

### ***1.1.3 Summary***

ADHD is a neurodevelopmental disorder that is characterised by age-inappropriate levels of inattention, hyperactivity and impulsivity. While diagnostic tools such as the DSM or the ICD define ADHD as binary, ADHD represents the extreme of a behaviour that varies continuously throughout the

population. A dimensional approach to ADHD may be beneficial for decreasing the risk of possible selection biases associated with clinical samples (Rutter et al., 1990) and for the investigation of the subclinical expressions of ADHD symptoms. A categorical approach may be adopted to study the clinical extreme as well as for ease of use, improved communication and consistency between clinicians and researchers. While parents and teachers typically rate ADHD symptoms in childhood and early adolescence, ADHD symptoms in late adolescence and adulthood are typically self-rated (Asherson, 2005).

## **1.2 Epidemiology**

ADHD is one of the most common psychiatric disorders worldwide, with the prevalence in children estimated at around 5-7% (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Thomas, Sanders, Doust, Beller, & Glasziou, 2015; Willcutt, 2012). Two recent meta-analyses concluded that, over the last thirty years, the number of children diagnosed with ADHD worldwide has remained constant (Polanczyk et al., 2014; Thomas et al., 2015).

As symptoms of ADHD tend to decline with age (Biederman, 2000; Faraone, Biederman, & Mick, 2006), ADHD was initially believed to be a childhood disorder (Barkley, 2008). However, ADHD is now recognised as frequently spanning from childhood into adolescence and adulthood (Cheung et al., 2015b; Faraone et al., 2006; Langley et al., 2010), with worldwide prevalence rates for adult ADHD ranging from 2.5% to 5% (Fayyad et al., 2007; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). The lower prevalence rates of adult ADHD compared to childhood ADHD may represent an underdiagnosis (Ginsberg, Quintero, Anand, Casillas, & Upadhyaya, 2014) and may be explained by methodological and diagnostic differences: ADHD symptoms in adult samples is often established using self-report measures only, diagnostic tools vary between studies and the mean age (20-30 years), as well as gender proportions, of most studies may not be representative of a typical adult population (Simon et al., 2009). In addition, until the publication of the DSM-5 (American Psychiatric Association, 2013), an adult ADHD diagnosis was based on symptom descriptions developed for children. This apparent lack of age-

appropriate ADHD symptom assessment has not only impeded clinical practice, but also research efforts (Brikell et al., 2015).

### ***1.2.1 Gender differences***

Gender differences in the prevalence of childhood ADHD are well documented in the literature, with higher rates of ADHD symptoms and diagnoses consistently reported for boys (Willcutt, 2012). Estimates of the worldwide male-to-female ratio in children with ADHD range from around 9:1 to 3:1 depending on whether the sample is a clinic-referred or population-based sample (Erskine et al., 2013; Gaub & Carlson, 1997; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Compared to studies of children with ADHD, there is an increased representation of females, and approximately equal distribution of males and females meeting diagnostic criteria, in studies of adult ADHD (Biederman et al., 1994; Biederman, Faraone, Monuteaux, Bober, & Cadogan, 2004; Rucklidge, 2010). One interpretation of these findings is that higher male-to-female ratios in childhood may represent the inadequacy of current diagnostic tools to ascertain ADHD in girls (Nussbaum, 2012). Current diagnostic criteria for ADHD have been developed on predominately male samples, which decreases their generalisability to female populations (Staller & Faraone, 2006).

An alternative explanation is that the underrepresentation of girls with ADHD arises from a gender-based referral bias. Girls, regardless of their diagnostic ADHD status, exhibit fewer disruptive behaviours and learning disabilities than boys (Biederman et al., 2002; Brassett-Harknett & Butler, 2007). Since these problems usually drive clinical referral, ADHD in girls may remain underidentified (Biederman et al., 2002; Brassett-Harknett & Butler, 2007). Support for this hypothesis comes from the finding that females are more likely than males to meet diagnostic criteria for ADHD-IA, whereas a larger proportion of males than females meet diagnostic criteria for ADHD-C (Willcutt, 2012). Inattentive symptoms may supposedly be less disruptive than combined-type or hyperactive-impulsive symptoms. As adults, however, an increasing number of women may self-refer to mental health services for attention problems (Arcia &

Conners, 1998; Biederman et al., 1994; Biederman et al., 2004), resulting in a more balanced gender distribution in clinical samples.

It is unclear whether gender differences in symptom severity exist. Whereas some studies have suggested that ADHD symptom severity is generally lower in females compared to males (Arnett, Pennington, Willcutt, DeFries, & Olson, 2015; Gaub & Carlson, 1997; Gershon, 2002), others have found either no differences (Das, Cherbuin, Butterworth, Anstey, & Eastaale, 2012; de Zwaan et al., 2012; Rasmussen & Levander, 2009; Retz-Junginger, Rösler, Müller, & Retz, 2012; Wilens et al., 2009) or increased symptom severity in females (Elkins, Malone, Keyes, Iacono, & McGue, 2011; Fedele, Lefler, Hartung, & Canu, 2010; Robison et al., 2008). It is conceivable that these inconsistencies result from the limited data available on female samples with ADHD.

### ***1.2.2 Co-occurring symptoms and disorders***

A high incidence of associated symptoms and disorders has been reported in both clinic-referred (Ghanizadeh, 2009; Skirrow & Asherson, 2013) and general population samples (Kadesjö & Gillberg, 2001; Kraut et al., 2013; Larson, Russ, Kahn, & Halfon, 2011). A recent study investigated co-occurring disorders of ADHD in 2,150,362 German insurees aged 3 to 17 years (Kraut et al., 2013). This study found that over 80% of methylphenidate users (a proxy for ADHD diagnosis; n=17,297) had at least one psychiatric comorbidity, compared to 20% of controls (Kraut et al., 2013). The most frequently co-occurring disorders in children and adolescents with ADHD were conduct disorder (CD) and oppositional defiant disorder (ODD). CD comprises a pattern of disruptive and violent behaviours, as well as recurrent violation of societal norms and rules (American Psychiatric Association, 2013). ODD describes an on-going pattern of uncooperative, defiant and hostile behaviours (American Psychiatric Association, 2013). Both clinical and epidemiological studies have investigated the association of CD and ODD with ADHD and found these disorders to co-occur in around 10-70% of children and adolescents with ADHD (Bauermeister et al., 2007; Freitag et al., 2012; Ghanizadeh, 2009, 2015; Jensen & Steinhausen, 2015; Kadesjö & Gillberg, 2001; Larson et al., 2011). While CD and ODD symptoms have been found to decline with age (Biederman et al.,

2008; Cumyn, French, & Hechtman, 2009), childhood CD and ODD are linked to worse long-term outcome with regards to academic and vocational achievement, rates of psychiatric comorbidities, ADHD symptom severity and functional impairment in adults with ADHD (Biederman et al., 2008; Harpold et al., 2007; Vitola et al., 2012).

Impairments in social communication and functioning are also common in both children and adults with ADHD. These impairments likely reflect the high rate of co-occurrence between ADHD and autism spectrum disorder (ASD), with 20-50% of those with ADHD also displaying ASD symptoms (Banaschewski, Poustka, & Holtmann, 2011; Lai, Lombardo, & Baron-Cohen, 2014; Polderman, Hoekstra, Posthuma, & Larsson, 2014; Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). Additionally, across the lifespan, ADHD is associated with anxiety and depression, which are characterised by excessive worry and fear and a disturbance in an individual's mood respectively (American Psychiatric Association, 2013). Anxiety disorders have been demonstrated in 20-35% of individuals with ADHD from both general population and clinical samples, while depressive disorders were found in 10-30% (Bauermeister et al., 2007; Biederman et al., 2012; Bloemsma et al., 2013; Hesson & Fowler, 2015). Furthermore, a systematic review suggested that 5-20% of adults with ADHD also meet diagnostic criteria for bipolar disorder (BD) (Asherson et al., 2014), but higher rates of 32% have also been reported (Halmøy et al., 2010). This discrepancy may arise because adult ADHD can resemble BD, especially the broader spectrum of BD, and vice versa. Consequently, ADHD and BD may be mistaken for one another or misdiagnosed as comorbid ADHD-BD due to the substantial symptomatic overlap (Asherson et al., 2014). The commonalities and differences between ADHD and BD are one of the topics of investigation in this thesis, and are discussed in more detail below (section 1.6 and chapter 2).

Children and adolescents with ADHD frequently exhibit difficulties with academic performance and achievement (Barkley, Murphy, & Fischer, 2010; Barry, Lyman, & Klinger, 2002; Frazier, Youngstrom, Glutting, & Watkins, 2007). In addition to behavioural problems, academic underachievement in individuals with ADHD may be attributed to specific learning difficulties such as dyslexia, dyscalculia and dysgraphia. A recent review found reading and numerical

disorders to occur in 24% to 38% and writing disorder to occur in 59% to 65% of children with ADHD (DuPaul, Gormley, & Laracy, 2013). ADHD is also associated with lower mean IQ scores. A meta-analysis of 123 studies estimated a 7–11-point difference in full-scale IQ between control individuals and individuals diagnosed with ADHD (Frazier, Demaree, & Youngstrom, 2004). The relationship between ADHD symptoms and IQ is a focus of this thesis and is discussed in more detail below (section 1.5.1 and chapter 5).

### ***1.2.3 Summary***

ADHD is one of the most common psychiatric disorders worldwide and frequently spans from childhood into adolescence and adulthood. While more boys than girls are diagnosed with ADHD, females make up approximately half of the ADHD population in adulthood. Reasons for this shift in male-to-female ratio from paediatric to adult samples remain elusive. A high incidence of co-occurring symptoms and disorders has been found in individuals with ADHD.

## **1.3 Treatments and interventions**

Since ADHD symptoms and impairments often persist from childhood into adolescence and adulthood, there is a continued need for treatment and management of the disorder across the lifespan. The National Institute for Health and Care Excellence (NICE) recommends group-based parent-training/education programmes and group-based psychological treatment, such as cognitive behavioural therapy (CBT) and/or social skills training, as first-line treatment for children with ADHD and moderate impairment (National Collaborating Centre for Mental Health, 2013). In adolescence, individual psychological treatment is recommended. Drug treatment may be considered as an alternative for children and adolescents with moderate impairment levels, who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group psychological treatment. While drug treatment is not indicated as the first-line treatment for children and adolescents with ADHD, it is recommended as the first-line treatment for adults with ADHD with either moderate or severe levels of

impairment. The psychostimulant methylphenidate is recommended as the first-line drug (National Collaborating Centre for Mental Health, 2013).

A robust evidence base stemming from randomised control trials attests to the efficacy of psychostimulant drugs as well as non-psychostimulant medication, such as atomoxetine, in reducing the symptoms and cognitive impairments associated with ADHD in children and adolescents (Abikoff et al., 2004; Brown et al., 2005; Garnock-Jones & Keating, 2009), as well as in adults (Faraone & Glatt, 2010; Moriyama, Polanczyk, Terzi, Faria, & Rohde, 2013; Surman, Hammerness, Pion, & Faraone, 2013). Some individuals may not respond to stimulant medication or atomoxetine and complete normalisation of symptoms is rare (Banaschewski et al., 2006). Stimulant medication and atomoxetine may also be less effective for treating disorders and symptoms that frequently co-occur with ADHD, such as conduct problems or anxiety disorders (see section 1.2.2 for more detail). Consequently, multimodal treatment plans including medication and psychological interventions, tailored to the specific needs of the patient, should be considered for the treatment of ADHD (National Collaborating Centre for Mental Health, 2013). While the benefits of multimodal treatment plans have been established in the Multimodal Treatment study of ADHD (MTA), the effects seem to dissipate on or shortly after termination of the treatment (Hinshaw & Arnold, 2015).

A variety of non-pharmacological interventions, such as psychological (cognitive training, neurofeedback, and behavioural training) and dietary (restricted elimination diets, artificial food colour exclusions, and free fatty acid supplementation) interventions, are also available. A recent meta-analysis found blinded evidence that behavioural interventions used to treat children and adolescents with ADHD, including behavioural training, social skills training and CBT, had beneficial effects on important aspects of child and parent functioning, namely decreasing comorbid childhood conduct problems and increasing positive parenting (Daley et al., 2014). Yet, the evidence for the efficacy of non-pharmacological treatment interventions on reducing ADHD symptoms is far from clear and limited by the unblind status of researchers and raters of behaviour (Sonuga-Barke et al., 2013). Blinded evidence for small but significant reductions in ADHD symptoms has so far only been found for free



fatty acid supplementation and artificial food colour exclusion (Sonuga-Barke et al., 2013). Identifying alternative non-pharmacological treatments on the basis of our growing understanding of the pathophysiology, as well as risk and protective factors of ADHD, is therefore essential.

One alternative treatment for ADHD that has gained increasing attention over the past few years is neurofeedback, which is rooted in findings of neurophysiological impairments in ADHD. In neurofeedback training, individuals with ADHD learn to match their neurophysiological profile more closely to that of typically developing children and to control certain aspects of their neural activity, such as attentional states, to modulate them on demand (Arns, Heinrich, & Strehl, 2014; Gevensleben et al., 2014). A meta-analysis including data from 10 prospective, controlled trials on children with ADHD ( $n=467$ ) reported large effect sizes for the effect of neurofeedback on inattention and impulsivity (Cohen's  $d=0.81$ ,  $d=0.68$  respectively) and a moderate effect size for the effect of neurofeedback on hyperactivity ( $d=0.39$ ) (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009). However, some of the studies included have been criticised for their methodological short-comings with regards to randomisation, appropriateness of the control groups, diagnostic criteria and blinding procedure (Holtmann, Sonuga-Barke, Cortese, & Brandeis, 2014). A more recent meta-analysis, therefore, applied a more stringent, selective approach and included only eight studies meeting high methodological standards (Sonuga-Barke et al., 2013). Results from this meta-analysis showed a moderate to large effect size (standard mean difference= $0.59$ ) for treatment effects of neurofeedback. This effect was reduced to moderate (standard mean difference= $0.29$ ) and trend level significance ( $p=0.07$ ) when properly blinded ratings were applied. Since these meta-analyses, several neurofeedback studies have been published with inconsistent results. While the quality of study design may have improved, non-standardised protocols and equipment still complicate the interpretation of these inconsistencies (Holtmann et al., 2014) and the efficacy of neurofeedback remains to be elucidated.

### ***1.3.1 Physical activity***

Another putative treatment target for ADHD that has garnered growing interest is physical activity (PA) (Rommel, Halperin, Mill, Asherson, & Kuntsi, 2013, see Appendix 1 for full publication). Animal research, as well as studies of typically developing children, adolescents and adults suggest that PA has the potential to improve ADHD symptoms and impairments associated with the disorder (Rommel et al., 2013). Both chronic and acute PA have been associated with improved EF in school-aged children with ADHD. One study investigating the effects of acute PA on EF reported that 30 minutes of moderate-intensity running facilitated performance on the colour-word condition of the Stroop task and certain aspects of the Wisconsin Card Sorting Test in 20 children with ADHD randomly assigned to the PA group, relative to 20 children with ADHD assigned to the control condition of watching an PA-related video (Chang, Liu, Yu, & Lee, 2012). However, PA did not have an effect on all measures of EF and effect sizes were small to moderate. Another study examining the impact of acute PA used a within-participant design to assess the effect of a 20-minute moderate-intensity bout of PA in 20 children diagnosed with ADHD and 20 healthy-matched controls (Pontifex, Saliba, Raine, Picchietti, & Hillman, 2012). Following PA, both the ADHD and the control group exhibited greater response accuracy on a version of the Eriksen flanker task, measuring inhibitory control, relative to a seated reading condition. Acute PA, therefore, seems to have at least some effect on certain tasks assessing EF. The effect of PA on EF seems to be universal and not specific to ADHD.

The impact of chronic PA on EF has been assessed by measuring the amount of moderate- to high-intensity PA performed by children with ADHD each day over a period of one week using an accelerometer (Gapin & Etnier, 2010). PA quantity significantly predicted performance on the Tower of London task, and was positively associated with working memory, inhibition and information processing in 18 boys with ADHD. Similarly, a six-week prospective trial of 12 bi-weekly sessions demonstrated that EF, as measured by the digit symbol test, as well as co-operativeness were significantly improved by PA relative to behavioural educational sessions in 28 boys with ADHD. While no significant changes were found with regards to hyperactivity scores, inattention scores

improved in the PA group (Kang, Choi, Kang, & Han, 2011). Furthermore, compared to 42 individuals with ADHD who did not receive an intervention, 42 individuals with ADHD partaking in a moderate-intensity 10-week PA programme of three sessions per week significantly improved on teacher-ratings of attention, motor skills and academic and classroom behaviour (Ahmed & Mohamed, 2011). Correspondingly, another study of the effects of a 10-week moderate-to-high-intensity PA programme on fitness, cognitive functions and ADHD-related behaviour in 10 children with ADHD reported significant improvements in muscular capacities, motor skills, level of information processing and parent- and teacher-rated social, thought and attention problems following the intervention compared a no-intervention control group consisting of 11 children with ADHD (Verret, Guay, Berthiaume, Gardiner, & Béliveau, 2012). The findings from studies investigating the effect of PA on ADHD suggest that PA may be beneficial for individuals with high levels of ADHD symptoms and associated impairments. Yet, more and better-quality evidence is needed to establish the impact of PA on ADHD symptoms and its efficacy in alleviating the symptoms and impairments associated with the disorder. The effect of PA on ADHD is a key focus of this thesis and is discussed in more detail in chapter 6.

### ***1.3.2 Summary***

While psychostimulant drugs and atomoxetine are efficacious in reducing the symptoms and cognitive impairments associated with ADHD across the lifespan, medication is less effective in treating the co-occurring disorders and symptoms. Moreover, medication does not develop vital organisational and social skills in individuals with ADHD, which could be applied upon completion of treatment. As a result of these shortcomings, the interest in alternative treatments, such as neurofeedback and physical activity, are growing. However, their efficacy and clinical value are still under investigation.

## **1.4 Aetiology of ADHD**

The past two decades have seen an upsurge in studies investigating the genetic and environmental factors influencing ADHD, its symptoms and

associated impairments. While quantitative and molecular genetic research has played a significant role in shaping our understanding of ADHD, results from these studies have also brought to light the aetiological complexity of the disorder. Findings from quantitative genetic studies have firmly established the high heritability of ADHD and provided insight into the aetiology of developmental effects, the underlying neurophysiology and the co-occurrence of ADHD with other disorders. The combined effect of environmental factors and multiple common genetic variants is hypothesised to contribute to ADHD risk. This chapter offers an overview of these issues, outlining molecular and quantitative genetic methods as well as summarising the overall pattern of findings.

### ***1.4.1 Quantitative genetics***

#### ***1.4.1.1 Sibling design***

Sibling studies have consistently reported a higher prevalence of ADHD symptoms and diagnoses in siblings of affected individuals, compared to siblings of typically developing children (Biederman, 2005), supporting the idea that familial factors play a significant role in mediating the susceptibility to ADHD. The sibling design allows the partitioning of variance in ADHD symptoms into familial and non-shared, based on the fact that siblings share, on average, 50% of their DNA, as well as sharing many aspects of their environment due to growing up in the same family (shared environment). An extension of the sibling design, the twin method (outlined below), allows a further separation of familial factors into genetic and shared environmental influences and also affords the investigation of non-shared environmental factors.

#### ***1.4.1.2 Twin design***

Twin studies constitute a powerful tool for disentangling the relative importance of environmental and genetic influences on ADHD. The classical twin design compares MZ twins with DZ twins (Rijsdijk & Sham, 2002). Both kinds of twin pairs experience the same amount of environmental similarity but their genetic resemblance differs. Whereas DZ twins share roughly half of their genetic

material, MZ twins are genetically identical at the DNA sequence level. Yet, both MZ and DZ twins are assumed to share many aspects of their environment by virtue of being born at the same time and place (shared environment, C). Thus, any difference between MZ twins can be attributed to so-called non-shared environmental influences (E; i.e. everything that makes MZ twins growing up in the same family different). E also includes measurement error. In accordance with these assumptions and definitions, twice the difference between MZ and DZ twin correlations allows for an estimation of the additive genetic effects (A) playing a role in shaping a certain phenotype. Moreover, a DZ similarity less than half the MZ similarity yields an estimate of the non-additive genetic effects (D) involved. Whereas univariate twin analysis can help disentangle environmental and genetic influences on ADHD, multivariate genetic analyses allow insights into the environmental and genetic effects on the overlap between ADHD and different traits. In multivariate twin analysis, MZ and DZ correlations are compared across traits: i.e. the correlation of one twin's score on a trait is compared with the co-twin's score on another trait. If the cross-trait cross-twin correlations are greater for MZ than for DZ twins, the implication is that genetic factors contribute to the phenotypic correlation between the two traits. This type of analysis also generates genetic and environmental correlations ( $r_A$ ,  $r_C$ ,  $r_E$ ), which can range from  $-1$  to  $1$ , and represent the extent to which genetic and environmental influences on two traits overlap (regardless of their individual heritabilities). Phenotypic correlations can also be attributed to genetic and environmental influences. The twin design will be applied in chapter 5 and its assumptions underlie the analysis in chapter 6.

#### *1.4.1.3 Quantitative genetic findings in ADHD*

Family studies have consistently reported higher prevalence of ADHD in parents and siblings of individuals diagnosed with ADHD compared to parents and siblings of typically developing children (Biederman, 2005). Adoption studies have also shown increased rates of ADHD in the biological parents of children with ADHD compared to both adoptive parents and parents of children without ADHD (Sprich, Biederman, Crawford, Mundy, & Faraone, 2000). Moreover, research has reported much higher concordance rates for ADHD in MZ than DZ twins (Thapar, Holmes, Poulton, & Harrington, 1999). Taken

together, these findings suggest that ADHD is a strongly heritable disorder. A review of 20 twin studies estimated the heritability of ADHD in children and adolescents at around 76% (Faraone et al., 2005). A subsequent meta-analysis provided a very similar estimate for broad (A+D) heritability of ADHD at around 70% (Burt, 2009). Lower heritability estimates ( $h^2 < 50\%$ ) found in adult populations have been attributed to potential self-rater measurement error (Larsson et al., 2013; Merwood et al., 2013; see section 1.1.2 for discussion). When self- and parent-ratings were combined to assess the heritability of ADHD symptoms in a large population-based sample of twins, heritability estimates at age 19-20 years ( $h^2 = 0.77-0.82$ ) mirrored those in childhood (Chang et al., 2013). Yet, many new genetic influences on ADHD symptoms appear to arise over the developmental course from childhood to adolescence, and may be contributing to some children remitting from ADHD, while others persist (Pingault et al., 2015).

Comparable heritability estimates for inattentiveness ( $h^2 = 71\%$ ) and hyperactivity-impulsivity symptoms ( $h^2 = 72\%$ ) have been established (Nikolas & Burt, 2010). With a genetic correlation of 0.55, over half of the genetic influences are shared between the two symptom dimension of ADHD, inattentiveness and hyperactivity-impulsivity (Greven, Asherson, Rijdsdijk, & Plomin, 2011; Larsson et al., 2013; McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007), while around 45% of the genetic influences are unique to each of the two symptom dimensions. These findings suggest that the two behavioural domains represent partially overlapping but partially separable symptom domains.

### ***1.4.2 Molecular genetics***

Quantitative genetic studies have conclusively demonstrated that genetic influences play a key role in the aetiology of ADHD. Consequently, a vast number of molecular genetic studies have set out to examine the way the ADHD phenotype could be mapped on to a genotype. Early research explored candidate genes from association or linkage studies to examine the relationship between a pre-specified gene of interest and ADHD. Most of these studies focused on genes associated with dopaminergic pathways known to be involved

in the clinical response to psychostimulant medication, or serotonergic systems which are implicated in brain networks of attention, memory and motor activities (Gizer, Ficks, & Waldman, 2009). A meta-analysis revealed that while significant associations were identified between ADHD and several candidate genes (e.g. DAT1, DRD4, DRD5 and 5-HTT), the effect sizes of these associations were small, with odds ratios ranging from 1.12 to 1.33 (Gizer et al., 2009).

Another approach taken to explore the genetic architecture of ADHD is the scanning of markers across the complete sets of DNA, or genome, of a large number of people to discover genetic variations associated with the disorder. This method, known as genome-wide association study (GWAS), has the potential to detect completely novel associations without the need for a priori hypotheses. Yet, childhood (Hinney et al., 2011; Lasky-Su et al., 2008; Mick et al., 2010; Neale et al., 2008; Neale, Medland, Ripke, Anney, et al., 2010; Stergiakouli et al., 2012; Yang et al., 2013) and adult GWAS (Lesch et al., 2008; Zayats et al., 2015), as well as a meta-analysis of the childhood studies (Ebejer et al., 2013; Neale, Medland, Ripke, Asherson, et al., 2010), have so far failed to identify common risk variants of genome-wide significance ( $p \leq 5 \times 10^{-8}$ ). A limitation of GWAS is that statistical power to detect associations is generally very low ( $\geq 80\%$  power) and, therefore, extremely large samples are required (Visscher, 2008). Consequently, the failure of ten ADHD-GWAS and one meta-analysis to uncover significant associations may, at least partly, be ascribed to too small samples, severe multiple testing corrections and the small effect sizes of individual risk loci (Hawi et al., 2015).

As a result, research on common genetic variants in ADHD has begun to consider common variants from GWAS as an aggregate, employing polygenic risk score analysis. Polygenic scores derived from individuals diagnosed with ADHD have been shown to predict affection status in an independent sample (Hamshere et al., 2013) and ADHD trait levels in a general population sample (Groen-Blokhuis et al., 2014; Martin et al., 2014). Furthermore, polygenic scores for ADHD trait levels in the general population are associated with ADHD diagnosis and symptom severity in individuals diagnosed with ADHD (Stergiakouli et al., 2015). This multi-factorial, or polygenic, approach to ADHD

is consistent with the high prevalence of ADHD in the general population, as well as with the high concordance rate in MZ twins (70-80%) but modest risk to first-degree relatives (~20%) (Hawi et al., 2015).

The limited success of GWAS has also spurred interest in rare genetic variation such as copy number variants (CNVs), which may contribute to ADHD. CNVs are large rare chromosomal structural abnormalities, i.e. gains and losses of large chunks of DNA sequence arising through non-allelic recombination or replication, that account for about 13% of the human genome (Stankiewicz & Lupski, 2010). These variations have been found to play a significant role in the aetiology of psychiatric disorders such as schizophrenia, BD and ASD (Cook & Scherer, 2008). Although existing research provides evidence for a role of CNVs in the aetiology of ADHD, the particulars of this role are yet to be established (Hawi et al., 2015).

### ***1.4.3 Environment***

Various environmental factors, such as maternal smoking and stress, as well as preterm birth and environmental toxins, are reportedly implicated in the aetiology of ADHD (Thapar, Cooper, Eyre, & Langley, 2013). Yet, these observed relationships may not be causal, but instead may arise from confounding genetic or familial factors (since parents provide both genetic and shared environmental influences). The consistently reported association between maternal smoking during pregnancy and increased risk for ADHD in the offspring, for example, can be attributed to unmeasured familial confounding (Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014). The relationship between maternal smoking during pregnancy and ADHD in the offspring was investigated in 813,030 individuals born in Sweden between 1992 and 2000. While maternal smoking predicted ADHD in the offspring, with hazard ratios (HRs) of 1.89 and 2.50 depending on how much the mother smoked, the association disappeared ( $HR=0.88-0.84$ ) when unmeasured confounders within the nuclear family (i.e., comparison between siblings) were taken into account (Skoglund et al., 2014).



The association of preterm birth with ADHD, on the other hand, seems to be largely independent of shared familial confounds and, therefore, potentially causal (D’Onofrio et al., 2013). A population-based cohort study, combining Swedish registries to identify all individuals born in Sweden from 1973 to 2008 (3,300,708 offspring of 1,736,735 mothers) reported a robust association between early gestation (23-27 weeks’ gestation) and ADHD diagnosis (hazard ratio, HR=2.3), independent of measured covariates and familial factors shared by siblings (D’Onofrio et al., 2013). Preterm birth is a key topic of this thesis and is discussed in more detail below (section 1.7; chapters 3 and 4).

#### ***1.4.4 Gene-environment interplay***

Previous research has demonstrated that both genetic and environmental influences play a part in the aetiology of ADHD. Yet, genes and environment do not operate in isolation (Nigg, Nikolas, & Burt, 2010; Purcell, 2002). Instead, a certain genotype may make an individual more susceptible to environmental risk or protective factors (gene-environment interaction) or may increase the likelihood of exposure to certain environmental influences (gene-environment correlation) (Purcell, 2002). Although clear evidence for gene-environment interplay has been found for other psychiatric disorders, such as depression (Caspi et al., 2003; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Thapar, Collishaw, Pine, & Thapar, 2012), only a small proportion of relevant genes and environments have been investigated for gene-environment interplay in ADHD and often findings from these studies have not been replicated (Nigg et al., 2010; Thapar et al., 2013).

Environmental factors may also influence genes more dynamically via epigenetic processes (Cortessis et al., 2012; Mill & Petronis, 2008), which regulate gene expression independently of the DNA sequence (Henikoff & Matzke, 1997). Epigenetic research is still very much in its infancy and very few studies have investigated the epigenetic mechanisms underlying ADHD (Nigg, 2012). Studies that have looked at the epigenetic changes in animal models of ADHD have shown that as well as producing ADHD-like behaviours, prenatal exposure to toxins can result in an increase of histone acetylation (Luo, Haworth, & Plomin, 2010) and methylation (Kim et al., 2014) in the rat brain.

Changes in histone acetylation and DNA methylation have also been shown in initial epigenetic studies of children with ADHD (van Mil et al., 2014; Xu et al., 2015). These findings suggest a role for gene-environment interplay in the aetiological pathway to ADHD. Yet, future research will have to substantiate these early findings.

### ***1.4.5 Summary***

Taken together, these findings suggest that a combination of genetic and environmental factors, none of which are individually necessary or sufficient, may lead to ADHD. While quantitative genetic research has shown that ADHD is highly heritable throughout the lifespan, results from molecular genetic studies highlight the aetiological complexity of ADHD. Several potential environmental risk factors have been identified. Interplay between genetic and environmental risk factors may contribute to susceptibility to ADHD or moderate the manifestation of the ADHD phenotype. Advances in analysis techniques may help to further unravel the heterogeneous and complex aetiology of ADHD in the future.

## **1.5 Cognitive and neurophysiological impairments in ADHD**

Evidence from quantitative and molecular genetic studies suggests that a large number of genes with small effect likely confer risk for ADHD (Smoller et al., 2013). Therefore, multiple pathways, both shared and unique, are likely to lead to the same symptoms or neurophysiological deficits. To advance our understanding of complex heterogeneous psychiatric conditions such as ADHD, research efforts are being dedicated to gaining insights into the pathways from the biological basis of the disease to the full clinical phenotype. Biological markers, or biomarkers, which are objectively measured indicators of a biological state or condition (Biomarkers Definitions Working Group, 2001), may not only help to elucidate the pathways and processes underlying ADHD, but may also inform us on the boundaries and overlap between current categorical definitions of ADHD and other associated disorders. Consequently, studying ADHD using multiple levels of intermediate measurements is likely an informative approach. An appreciation of the cognitive and neurophysiological

processes underlying ADHD may not only improve diagnosis but also intervention, prognosis and prevention of ADHD. The following section offers a review of the key cognitive and neurophysiological impairments of ADHD.

### ***1.5.1 Phenotypic studies of cognitive impairments***

Impairments in executive functioning (EF) resulting from dysfunction in the fronto-striatal region of the prefrontal cortex have long been conceptualised as being a central deficit of ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). EF is an umbrella term comprising various higher cognitive functions such as response inhibition, planning, problem solving and working memory (Barkley, 1997; Castellanos & Tannock, 2002). A meta-analysis found moderate effect sizes ( $d=0.46-0.69$ ) for the association between ADHD and impairments in various EF domains, namely response inhibition and working memory (Willcutt et al., 2005).

Sustained attention, which is the maintenance of focused attention over an extended period of time, can be assessed using the continuous performance test (CPT, see section 2.3.2 for task description). The CPT requires participants to detect target stimuli among a sequence of distractor stimuli. Omission errors (OE; the lack of a response to a target) are assumed to represent impairments in sustained attention. Other performance measures that can be obtained from the CPT are reaction time variability (RTV), which is defined as intra-individual fluctuations in reaction times during task performance, and commission errors (CE), which are responses to non-target stimuli. CEs are an index of response inhibition. Whereas the CPT can indicate response inhibition with the help of CEs, it is designed to measure sustained attention. Response inhibition is better assessed using a Go/NoGo task. The reason for this is the target-to-non-target ratios of these two tasks, which is low for the CPT (few targets and many distractors) and high for the Go/NoGo task (many targets and few distractors). The CPT is, therefore, more likely to lead to OEs, while the Go/NoGo task is more likely to lead to CEs.

A recent meta-analysis examining 47 studies of CPT performance in children with ADHD found increased OE, CE and RTV in children with ADHD compared

to typically developing controls, with moderate-to-large effect sizes ( $d=0.62$ ,  $d=0.55$  and  $d=0.56$  respectively) (Huang-Pollock, Karalunas, Tam, & Moore, 2012). Similarly, a meta-analysis of Go/NoGo performance in 30 studies of children with ADHD found a moderate-to-large effect for CE, with the standard mean difference ranging from 0.37 to 0.57 (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). In adults with ADHD, similar deficits have been reported, including problems in sustained attention (Antshel et al., 2010; Gallagher & Blader, 2001; Lijffijt, Kenemans, Verbaten, & Van Engeland, 2005; Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007) and response inhibition (Bekker et al., 2005; Bekker et al., 2005; Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2010; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Lampe et al., 2007; Lijffijt et al., 2005). These findings provide support for the notion that impairments in sustained attention and response inhibition are important features of ADHD across development.

In addition, a recent meta-analysis of 319 studies established a large effect size for RTV in children and adolescents with ADHD (Hedges'  $g=0.76$ ) and a moderate effect size for RTV in adults with ADHD ( $g=0.46$ ) relative to typically developing controls (Kofler et al., 2013). The size of the effect suggests that RTV is a relatively ubiquitous and stable feature of ADHD. Yet, reaction time impairments in ADHD are sensitive to task condition. As such individuals with ADHD demonstrate significantly greater improvements in the consistency of their responses under relatively stimulating (fast-rewarded) task conditions compared to controls (Andreou et al., 2007; Cheung et al., 2015a; Kuntsi et al., 2013; Uebel et al., 2010). This suggests that, rather than being a stable cognitive deficit, increased RTV in ADHD is a malleable and dynamic impairment, which could be explained by difficulties in arousal regulation or the allocation of sufficient neuronal resources (Sergeant, 2005).

Another cognitive impairment linked to ADHD is lower general cognitive ability. Correlations between ADHD symptoms and IQ scores have been reported to range from  $-0.2$  to  $-0.4$  in population-based samples (Kuntsi et al., 2004; Wood, Asherson, Van Der Meere, & Kuntsi, 2010). Furthermore, a meta-analysis of 123 studies estimated a 7–11-point difference in full-scale IQ between control individuals and individuals diagnosed with ADHD (Frazier et al.,

2004). Lower IQ scores have been linked to increased severity of ADHD symptoms (Grizenko, Qi Zhang, Polotskaia, & Joobar, 2012), higher levels of externalising and behavioural problems in individuals diagnosed with ADHD (Ahuja, Martin, Langley, & Thapar, 2013), as well as worse long-term outcome (Cheung et al., 2015b). On the contrary, higher IQ has been shown to positively impact the response to pharmaceutical treatment in ADHD (Aman, Buican, & Arnold, 2003; Hinshaw, 2007; Owens et al., 2003; van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). The association between ADHD and IQ is a focus of this thesis and is discussed in more detail below (chapter 5).

### ***1.5.2 Quantitative genetic studies of cognitive impairments in ADHD***

Impairments in EF, such as response inhibition, and RTV, have been reported in unaffected siblings of individuals diagnosed with ADHD (Andreou et al., 2007; Bidwell, Willcutt, Defries, & Pennington, 2007; Chen et al., 2008; Crosbie & Schachar, 2001; Gau & Shang, 2010; Goos, Crosbie, Payne, & Schachar, 2009; Lin, Hwang-Gu, & Gau, 2015; Loo et al., 2008; Nikolas & Nigg, 2015; Pironti et al., 2014; Slaats-Willemse, Swaab-Barneveld, De Sonneville, & Buitelaar, 2007; Uebel et al., 2010). Furthermore, univariate twin analysis has revealed moderate genetic influences for reaction time, inhibition and working-memory performance (Kuntsi et al., 2006).

With regard to IQ, the negative association with ADHD can largely be attributed to genetic factors. One twin study reported that 86% of the phenotypic correlation between ADHD symptom and IQ scores and 100% of the association between ADHD research diagnosis and IQ scores were accounted for by genetic factors, with genetic correlations of  $r_A = -0.45$  between IQ and ADHD symptoms and  $r_A = -0.59$  between IQ and ADHD research diagnosis (Kuntsi et al., 2004). Significant genetic correlations have also been found in other population-based twin samples (Greven, Kovas, Willcutt, Petrill, & Plomin, 2014; Paloyelis, Rijdsdijk, Wood, Asherson, & Kuntsi, 2010; Polderman et al., 2006; Wood, Asherson, et al., 2010). Multivariate model fitting analyses in both family (Rommelse et al., 2008; Wood et al., 2011) and twin studies (Wood, Asherson, et al., 2010) have revealed that the aetiological influences shared between ADHD and IQ largely separate from the aetiological influences on

ADHD and other cognitive impairments. While the shared genetic origins of ADHD and IQ are well documented, little is known about the direction of effects or the genetic overlap between these variables at different developmental stages. Chapter 5, therefore, focuses on the developmental and aetiological patterns of the association between ADHD symptoms and IQ in a population-based sample of twins.

The overall genetic architecture underlying the various cognitive impairments associated with ADHD may best be conceptualised using multivariate investigations. In a multivariate familial analysis of a large sample of ADHD and control sibling pairs ( $N=1,265$ ), two familial cognitive impairment factors emerged (Kuntsi et al., 2010). The larger factor, accounting for 85% of the familial variance of ADHD, captured 98-100% of the familial influences on mean reaction time and RTV. The second, smaller factor, reflecting 13% of the familial variance of ADHD, captured 82% of the familial influences on OE and 62% of those on CE on the Go/NoGo task. A similar pattern of results emerged in an investigation of 238 ADHD families (350 ADHD-affected and 195 non-affected children) and 147 control families (271 children), which also yielded two familial cognitive impairment factors (Frazier-Wood et al., 2012). IQ was not related to the first familial factor shared with reaction time data, but a portion (33%) of the familial influences on IQ were shared with the second factor, capturing working memory. Moreover, in a large sample of ADHD and control sibling pairs a significant familial association between cognitive performance, including MRT and RTV, and both ADHD and IQ emerged (Wood et al., 2011). Again, the association between ADHD and cognitive performance was largely independent (80-87%) of any contribution from aetiological factors shared with IQ.

Results from a recent twin study further revealed that the association between ADHD and RTV reflects largely genetic influences that RTV shares with inattention (Kuntsi et al., 2014). In line with aetiological separation of these cognitive impairments, no significant shared genetic influences across RTV and CE ( $r_A=-0.03$ ) emerged. Taken together these findings suggest aetiological separation of cognitive processes in ADHD, with one familial cognitive factor capturing executive control (inhibition, working memory) and separating from another familial cognitive factor capturing the slow and highly variable

responses (Frazier-Wood et al., 2012; Kuntsi et al., 2010). Both of these familial factors largely separate from the aetiological influences ADHD symptoms share with IQ (Frazier-Wood et al., 2012; Rommelse et al., 2008; Wood, Asherson, et al., 2010; Wood et al., 2011).

### ***1.5.3 Phenotypic studies of neurophysiological impairments in ADHD***

Electroencephalography (EEG) provides an index of neural activity by measuring electrical activity along the scalp. The resulting electrophysiological parameters offer excellent temporal resolution, allowing for precise analysis of atypical oscillation patterns as well as neurophysiological processes underlying cognitive impairment.

#### ***1.5.3.1 Quantitative EEG***

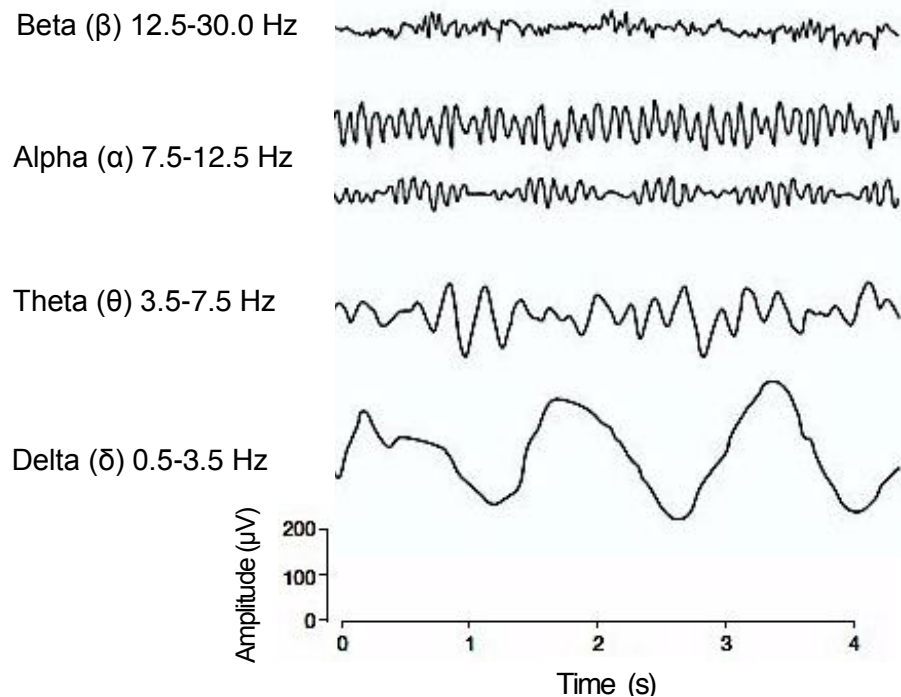
Neural activity shows oscillations at a range of frequencies. Frequency is the number of oscillations per unit time and is measured in hertz (Hz), where 1 Hz describes one oscillation per second. Electrophysiological recordings are traditionally quantified into the frequency bands delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz) and gamma (>30 Hz) (Tye, McLoughlin, Kuntsi, & Asherson, 2011) (Figure 1.1). These frequency bands have demonstrated high test-retest reliability (0.71-0.95), particularly the theta and delta bands (>0.85) (Williams et al., 2005). Quantitative EEG (QEEG) measures the strength of the electrical activity (EEG power in  $\mu\text{V}$ ).

QEEG studies in children, adolescents and adults with ADHD have established atypical oscillation patterns in individuals with ADHD (Arns, Conners, & Kraemer, 2013). Increased power in slow (mainly theta) and decreased power in fast (mainly beta) frequency bands, as well as a higher proportion of slow to fast frequencies in the brain, as reflected by the theta:beta ratio (TBR), during resting-state conditions are the most frequently cited findings in relation to ADHD (Bresnahan, Anderson, & Barry, 1999; Bresnahan & Barry, 2002; Clarke et al., 2003a, 2006, 2008; Cooper et al., 2014; Koehler et al., 2009; Snyder & Hall, 2006). These results were initially reinforced by a meta-analysis that claimed an effect size of 3.08 for the TBR in ADHD, which was proposed to have sensitivity and specificity of 94% (Snyder & Hall, 2006). A subsequent

study by the same research group described 87% sensitivity, 94% specificity, and 89% overall accuracy of TBR for ADHD diagnosis, which was relatively independent of co-occurring psychiatric disorders, developmental level (childhood and adolescence), gender and race (Snyder et al., 2008). However, the increased TBR as a marker of ADHD diagnosis is now considered controversial (Jeste, Frohlich, & Loo, 2015), as several recent studies have failed to replicate high TBRs in ADHD (Buyck & Wiersema, 2014; Liechti et al., 2013; Loo et al., 2009; Ogrim, Kropotov, & Hestad, 2012; Poil et al., 2014; Skirrow et al., 2015). These negative findings were further reinforced in a recent meta-analysis, which concluded that excessive TBR could not be considered a reliable diagnostic measure of ADHD (Arns et al., 2013). Moreover, the meta-analysis demonstrated a significant highly negative correlation ( $r=-0.97$ ,  $p<0.001$ ) between year of publication and TBR effect size, indicating a significant decline in support for the TBR in ADHD over time. The authors attributed this decline to an increase in the TBR among control participants (possibly due to decreased sleep duration), which attenuates the TBR difference between individuals with ADHD and typically developing individuals (Arns et al., 2013). Other sources of difference may lie in uncontrolled developmental factors (i.e. age differences in samples) (Buyck & Wiersema, 2014; Poil et al., 2014) and the heterogeneity of ADHD (Jeste et al., 2015).

EEG research has indicated elevated resting delta and theta power in younger compared to older typically developing children (Benninger, Matthis, & Scheffner, 1984; Gasser, Jennen-Steinmetz, Sroka, Verleger, & Möcks, 1988; Gasser, Verleger, Bächer, & Sroka, 1988; Michels et al., 2013). Consequently, elevation of delta and theta power has been thought to represent immaturity of the brain. This has led to the development of a maturational-lag hypothesis of ADHD (Kinsbourne, 1973), which holds that there is a delay in central nervous system (CNS) development in individuals with ADHD as fast wave activity replaces slow wave activity. Yet, research demonstrating elevated theta power in adults with ADHD (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke et al., 2008; Koehler et al., 2009; Skirrow et al., 2015) do not support this hypothesis.





**Figure 1.1. EEG frequency bands commonly investigated in ADHD.**

Adapted from “Electrophysiological markers of genetic risk for attention deficit hyperactivity disorder” by C. Tye, G. McLoughlin, J. Kuntsi and P. Asherson, 2011, *Expert Reviews in Molecular Medicine*, 13, p.4, Copyright 2011 by Cambridge University Press. Reprinted with permission.

Elevated theta power during resting-state conditions in individuals with ADHD has been interpreted as representing cortical underarousal (Lubar, 1991; Satterfield & Dawson, 1971), because of its association with drowsiness (Makeig & Jung, 1996). Yet, no relationship between resting theta power and skin conductance levels (another marker of CNS arousal) has been found in children with and without ADHD (Barry et al., 2004; Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009). Consequently, it is not fully understood what increased theta power during resting-state conditions in ADHD represents. Nevertheless, increased theta power seems to be a relatively consistent marker of ADHD (McLoughlin, Palmer, Rijdsdijk, & Makeig, 2014).

QEEG studies of individuals with ADHD conducted during cognitive tasks have yielded less consistent results. One study reported elevated theta and decreased alpha power (El-Sayed, Larsson, Persson, & Rydelius, 2002) in children with ADHD (n=36) compared to controls (n=63) in both resting-state and cognitive task condition (CPT). Attenuated alpha power in the ADHD group compared to controls during a resting-state and a cognitive task condition (CPT)

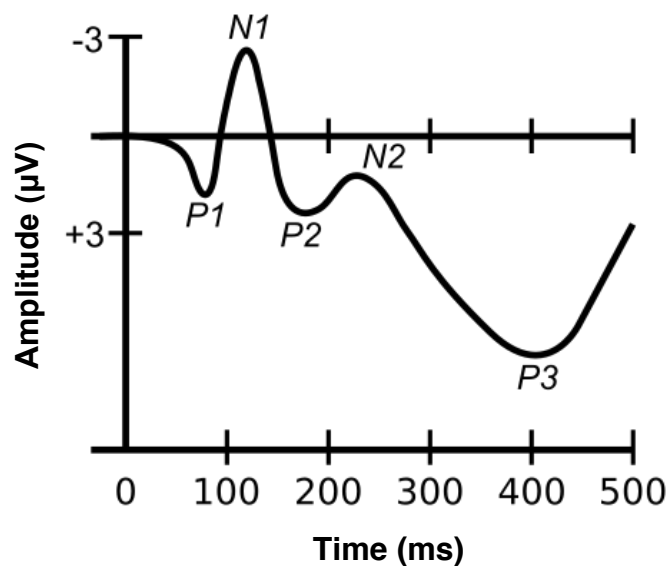
was also found in a study which investigated the EEG patterns of adults with ADHD (n=38) and controls (n=42) (Loo et al., 2009). Yet, other studies have reported an increase in alpha power in individuals with ADHD compared to controls when shifting from resting-state to cognitive task (CPT) condition (Nazari, Wallois, Aarabi, & Berquin, 2011; Swartwood, Swartwood, Lubar, & Timmermann, 2003). One study found no differences in cortical activity patterns of adults with ADHD (n=41) compared to controls (n=48) during a CPT (Skirrow et al., 2015). Instead, individuals with ADHD demonstrated lower theta power compared to controls during the Sustained Attention to Response Task (SART). These discrepancies may result from diverging sample characteristics, such as age and IQ, as well as from methodological differences. A recent study investigating QEEG differences between adolescents with ADHD (n=76) and controls (n=85) at the beginning and the end of a 1.5 h long testing session provided evidence for time-context effects. Whereas at the beginning of the testing session delta and theta power were increased in the ADHD group compared to controls, at the end of the session ADHD was associated with greater activity in the beta band relative to controls (Kitsune et al., 2015). The findings may represent short-term fluctuations in arousal during long experimental sessions and highlight the importance of recording context on resting-state QEEG data.

#### *1.5.3.2 Event-related potentials*

Event-related potentials (ERPs) are small voltage fluctuations in response to a cognitive, sensory or affective stimulus (or 'event'), which are averaged across multiple trials and time-locked to the event. Averaging across trials increases the signal-to-noise ratio by removing random background EEG signals. Moreover, averaging provides a measure of neural activity that is consistently linked to event processing in a time-locked fashion. The nomenclature of individual ERP components is often dictated by their polarity, where 'P' stands for positive and 'N' stands for negative, as well as their order of occurrence within the waveform (P1, N1, P2, N2, etc.) (see Figure 1.2).

The high temporal resolution and time-locked nature of ERPs provide an ideal medium to investigate covert neurocognitive processes, such as the

neurophysiological impairments underlying poor attention and response inhibition in individuals with ADHD (see section 1.5.1). ERP components of sustained attention and response inhibition have shown moderate to high long-term test-retest reliability, ranging from 0.56 to 0.92 (Fallgatter, Aranda, Bartsch, & Herrmann, 2002; Weinberg & Hajcak, 2011). CPTs (see section 2.3.2 for task description) have been employed frequently to investigate attentional processes and response inhibition using ERPs. CPTs yield electrophysiological indices of attentional orienting (Cue-P3, Cue-P2), response preparation (contingent negative variation; CNV), response execution at targets (Go-P3), conflict monitoring (NoGo-N2), and response inhibition (NoGo-P3) (Tye et al., 2011).



**Figure 1.2. Simulated ERP waveform showing several ERP components according to the typical naming conventions.** Negative voltages are plotted upwards. Adapted from “The Neurocognitive Networks of the Executive Functions” by S. Rusnáková and I. Rektor, 2012, In I.M. Ajeena (Ed.) *Advances in Clinical Neurophysiology*, p.165. The image is available under the Creative Commons license.

In line with findings from cognitive studies, which showed that CPT performance is typically impaired in individuals with ADHD, children (Albrecht et al., 2013; Banaschewski et al., 2003, 2008; Hennighausen, Schulte-Körne, Warnke, & Remschmidt, 2000; Perchet, Revol, Fournieret, Mauguière, & Garcia-Larrea, 2001; Tye, Asherson, et al., 2014; van Leeuwen et al., 1998) and adults with ADHD (McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011; Valko et al., 2009; Woltering, Liu, Rokeach, & Tannock, 2013) have shown reduced Cue-P3 and CNV amplitudes in response to cue stimuli, reflecting impaired attentional orienting and response preparation respectively. While an 11-year

follow-up study of these ERP components in individuals with ADHD (n=11) and controls (n=12) indicated that only the CNV continued to show a reduced amplitude in young adults with ADHD (mean age=21.9 years) compared to controls (mean age=21.1 years) (Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013), a meta-analysis of the Cue-P3 conducted across six studies in adults also revealed reduced Cue-P3 amplitude in adults with ADHD (n=154, mean age=27.6) compared to controls (n=140, mean age=26.2) with a medium effect size (Cohen's  $d=-0.55$ ) (Szuromi, Czobor, Komlósi, & Bitter, 2011). These inconsistencies may arise due to limited power in the longitudinal study, as 8 out of 11 participants with ADHD no longer met full ADHD diagnosis at follow-up (Doehnert et al., 2013). Less is known about the association of ADHD with ERP latencies. Whereas some studies have found reduced Cue-P3 latency in ADHD (McLoughlin et al., 2010), others have reported no differences between individuals with and without ADHD (Albrecht et al., 2013).

Following a cue, response control is required. Whereas Go-trials entail a response, the response on NoGo-trials needs to be suppressed. These task demands are reflected in the ERP components Go-P3 and NoGo-P3 respectively. Few studies have directly investigated the Go-P3, reflecting response execution, in individuals with ADHD. Those studies that have examined the Go-P3 in individuals with ADHD have reported an attenuated Go-P3 amplitude (Banaschewski et al., 2004; Lawrence et al., 2005; Overtom et al., 1998; Strandburg et al., 1996). The NoGo-P3, indexing response inhibition, on the other hand, represents a persistent neurophysiological deficit in ADHD and consistently shows reduced amplitude in children (Albrecht et al., 2013; Banaschewski et al., 2003; Brandeis, van Leeuwen, Steger, Imhof, & Steinhausen, 2002; Fallgatter et al., 2004, 2005; Tye, Asherson, et al., 2014; van Leeuwen et al., 1998) and adults with ADHD (Dhar, Been, Minderaa, & Althaus, 2010; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011; Valko et al., 2009). Taken together, findings from ERP amplitudes elicited by the CPT suggest impaired attentional and preparatory brain processes as well as deficits in response inhibition in both children and adults with ADHD.

Performance monitoring has also been proposed to be impaired in ADHD (Geburek, Rist, Gediga, Stroux, & Pedersen, 2013; Shiels & Hawk, 2010).

Go/NoGo and flanker tasks are commonly used to examine performance monitoring. The ERP components obtained from these tasks vary with task demands and accuracy of response. An N2 component, indexing performance monitoring, is obtained following a correct response to a target stimulus, while an error-related negativity (ERN or Ne) component is elicited by an erroneous response. Conscious processing of an erroneous response is reflected in the Pe component. Conversely, the ERN is thought to represent unconscious error monitoring.

Inconsistent findings have emerged with regards to conflict and error monitoring in individuals with ADHD. Reduced N2 amplitude has been reported in children (e.g. Albrecht et al., 2008; Broyd et al., 2005; Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006; Wild-Wall, Oades, Schmidt-Wessels, Christiansen, & Falkenstein, 2009), adolescents (Gow et al., 2012) and adults (McLoughlin et al., 2009) with ADHD. However, some studies have not found a difference in N2 amplitude between individuals with ADHD and controls (Fisher, Aharon-Peretz, & Pratt, 2011; Johnstone & Galletta, 2013; Jonkman, van Melis, Kemner, & Markus, 2007; Wiersema, van der Meere, Antrop, & Roeyers, 2006). Furthermore, a review of nine studies found that four studies demonstrated a reduction in ERN amplitude in children with ADHD compared to controls, while the same number of studies did not, and one study even found an increase in ERN amplitude in children with ADHD relative to controls (Shiels & Hawk, 2010). The review concluded that a reduction in Pe amplitude was a more robust finding in children with ADHD, with five studies reporting reduced Pe amplitude in children with ADHD and two studies failing to replicate these findings. While the results of adolescent and adult studies have also been inconsistent, a recent meta-analysis of seven studies reported that Ne/ERN amplitude was reduced in adolescents and adults with ADHD ( $n=166$ ) compared to controls ( $n=161$ ), with a moderate effect size of Cohen's  $d=0.50$  (Geburek et al., 2013). A moderate effect size (Cohen's  $d=0.42$ ) was also found for the attenuation of Pe in the ADHD group compared to controls, but this effect only showed trend level significance ( $p=0.052$ ). In line with these findings, two recent studies have reported both ERN and Pe attenuation in children with ADHD on both Go/NoGo (Groom et al., 2013) and flanker tasks (Rosch and

Hawk, 2013). Further research is needed for clarification and to identify the sources of variation in the literature. Inconsistencies may arise due to differences in sample size, clinical subtypes, comorbidity, task conditions and analysis (Shiels & Hawk, 2010). Overall, however, the results hint at a monitoring and response control deficit in individuals with ADHD.

#### *1.5.3.3 Quantitative genetic studies of neurophysiological impairments in ADHD*

Quantitative genetic studies have established that EEG parameters have high heritability, with heritability for all frequency bands ranging from 70% to 90% (Van Baal, De Geus, & Boomsma, 1996; van Beijsterveldt, Molenaar, de Geus, & Boomsma, 1996) and heritability for ERP components ranging from 41% to 60% (Anokhin, Heath, & Myers, 2004; van Beijsterveldt & van Baal, 2002). Moderate-to-high sibling correlations for EEG spectral power initially indicated familiarity of EEG measures in families affected by ADHD (Loo et al., 2010). Familial effects with ADHD have also been observed for attentional, preparatory and inhibitory processes, as indexed by the Cue-P3, CNV and NoGo-P3 respectively, and weaker error and conflict monitoring, as indexed by reduced ERN and the N2 components respectively, in both child (Albrecht et al., 2008, 2010, 2013) and adult ADHD samples (McLoughlin et al., 2009; McLoughlin, Asherson, et al., 2011).

Few twin studies have investigated the shared aetiological pathway between ADHD and neuropsychological impairments. However, substantial genetic overlap between ADHD symptoms and elevated theta power ( $r_A=0.35$ ) has been established (Tye, Rijdsdijk, & McLoughlin, 2014). In addition, a recent multivariate twin analysis found shared genetic influences between ADHD symptoms, frontal midline theta activity and RTV, with genetic correlations ranging from  $r_A=0.39$  to  $-0.61$  (where a negative genetic correlation reflects that the genetic influences resulting in lower mean theta amplitude lead to increased ADHD symptoms) (McLoughlin, Palmer, et al., 2014). A small genetic overlap ( $r_A=-0.15$ – $-0.22$ ) between the Go-P3 and externalising problems associated with ADHD (e.g. substance abuse, CD and antisocial behaviour) has also been demonstrated (Gilmore, Malone, & Iacono, 2010; Hicks et al., 2007).

### **1.5.4 Summary**

Research into the cognitive and neurophysiological impairments associated with ADHD is starting to elucidate the neurobiological basis underlying the clinical phenotype. The understanding gained from this research may in the future aid the development of biologically informed diagnostic criteria to improve interventions, prognosis and prevention. ADHD is linked to impairments in EF such as response inhibition and sustained attention, as well as to deficits in general cognitive ability (i.e. IQ). The phenotypic associations between ADHD and cognitive impairments are partly accounted for by genetic factors.

EEG and ERPs have been useful tools in the investigation of the neurophysiological impairments of ADHD. Individuals with ADHD show atypical oscillatory activity during resting-state and cognitive task conditions. While findings are mixed, elevated theta power during resting-state conditions is the most consistently reported EEG-abnormality in ADHD. Furthermore, findings from ERP studies suggest impaired attentional (P3 components) and preparatory (CNV) brain processes, as well as deficits in response inhibition (NoGo-P3) and performance monitoring (N2, ERN/Ne and Pe) in both children and adults with ADHD. Familial and genetic overlap of these neurophysiological impairments with ADHD has been demonstrated, but more research is needed to fully determine the familial and genetic associations of these variables with ADHD.

## **1.6 Bipolar disorder**

According to DSM criteria, bipolar disorder (BD) denotes a psychiatric condition that is distinct from ADHD (American Psychiatric Association, 2013). Yet, uncertainties regarding diagnostic boundaries between these two disorders arise from symptomatic overlap. Direct comparisons across ADHD and BD on cognitive-neurophysiological measures are limited, despite their potential utility to inform us on impairments that are specific to or shared between the disorders and, therefore, potential biomarkers that may aid in the identification of the diagnostic boundaries.

### ***1.6.1 Clinical symptoms and epidemiology***

BD denotes episodic and recurrent pathological disturbances in mood, ranging from severe depression to extreme elation (mania), including periods of normal mood (euthymia), although not necessarily a return to full function (Müller-Oerlinghausen, Berghöfer, & Bauer, 2002). A depressive episode is a period of pervasive and persistent low mood and/or a profound loss of interest and pleasure (American Psychiatric Association, 2000). A manic episode is defined as a distinct period during which patients experience abnormally and persistently raised, expansive, or irritable mood along with decreased need for sleep, grandiose ideas, impulsive behaviour, increased talkativeness, heightened activity and distractibility. Fifty per cent of episodes last between two and seven months (Angst & Sellaro, 2000). The mood disturbances are often accompanied by disturbances in thinking and behaviour as well as psychotic features such as delusions and hallucinations in more severe cases (American Psychiatric Association, 2000).

BD is a heterogeneous disorder presenting with varying degrees and expressions of mania and depression (American Psychiatric Association, 2000; Merikangas et al., 2011) and is, therefore, best conceptualised as 'bipolar spectrum' (Ghaemi, 2013). BD is categorised into bipolar I disorder (BD-I), bipolar II disorder (BD-II) and cyclothymia. The DSM-IV defines BD-I as one or more manic episodes, or mixed episodes of mania and depression, lasting a week or more. A diagnosis of BD-II requires one or more hypomanic episodes (similar to mania but not severe enough to cause marked social or occupational impairment) lasting at least four days and one or more major depressive episode. Cyclothymia is characterised by hypomanic episodes, alternating with episodes of mild or moderate depression (American Psychiatric Association, 2000). Although diagnostic criteria for BD remain largely unchanged in the DSM-5, the diagnosis of mania or hypomania now requires an individual to present with "persistently increased goal-directed activity or energy" (American Psychiatric Association, 2013).

BD is thought of as an adult disorder, with approximately half the cases retrospectively reporting disorder onset before age 25 years (Kessler et al., 2005; Merikangas et al., 2011; Post et al., 2008). In a survey of 61,392 adults



from the general populations of 11 countries in the Americas, Europe, and Asia, worldwide lifetime prevalence was estimated at 0.6% for BD-I, at 0.4% for BD-II and at 2.4% for bipolar spectrum (Merikangas et al., 2011). While in this study BD prevalence differed widely by country (with the highest lifetime prevalence of 4.4% in the USA and the lowest lifetime prevalence of 0.1% in India) (Merikangas et al., 2011), a review by the World Health Organisation of several other population surveys suggested that BD had comparable prevalence, ranging from 0.2% to 2.1%, across different regions of the world, including Europe, North America, Oceania, Africa, and South Asia (Ayuso-Mateos, 2006).

Comorbidities are common in BD, with over three-quarters of affected individuals also meeting criteria for another lifetime disorder (Merikangas et al., 2007, 2011). Anxiety disorders are the most common co-occurring conditions in individuals with BD, with comorbidity rates of around 60%. Externalising disorders, such as ADHD (~20%) and CD (~20%), as well as substance use disorders (~40%) also frequently co-occur in individuals with BD (Merikangas et al., 2011).

#### *1.6.1.1 Gender differences*

Aggregated results from 12 population surveys from around the world suggested that equal proportions of men and women are affected by BD (Ayuso-Mateos, 2006). More recently, a study of 61,392 adults from 11 countries reported greater lifetime prevalence rates of BD-I and sub-threshold BD in males than females, and higher rates of BD-II in females than males (Merikangas et al., 2011). A multisite seven-year follow-up study (n=711) by the Stanley Foundation Bipolar Treatment Outcome Network found that likelihood of having depressive symptoms was significantly greater for women than for men with BD (Altshuler et al., 2010), explaining the higher prevalence of BD-II in females. In addition, rapid cycling forms of BD-I and II may be more common in women (Schneck et al., 2004). In men, higher rates of co-occurring disorders have been reported (Hendrick, Altshuler, Gitlin, Delrahim, & Hammen, 2000; Kawa et al., 2005; Kessing, 2004).

### *1.6.1.2 Overlap with ADHD*

The comorbidity between BD and ADHD is well documented in the literature (Bernardi et al., 2012; Faraone et al., 1997; Hensch, Himmerich, & Hegerl, 2011; Klassen, Katzman, & Chokka, 2010; Lus & Mukaddes, 2009; Masi et al., 2006; Merikangas et al., 2011). Family and twin studies have provided evidence for the importance of genetic influences on susceptibility to BD (as well as ADHD, see section 1.4.1.3) and for its genetic and phenotypic complexity (Craddock & Sklar, 2009). A meta-analysis of family studies has also shown a significantly higher prevalence of ADHD among relatives ( $n=4,301$ ) of individuals with BD (relative risk;  $RR=2.6$ ) and a significantly higher prevalence of BD among relatives ( $n=1,877$ ) of individuals with ADHD ( $RR=1.8$ ) (Faraone, Biederman, & Wozniak, 2012). These findings suggest that ADHD and BD aggregate in families at higher-than-expected rates. The largest genome-wide analysis of psychiatric illness to date provided support for this assumption by demonstrating that common genetic variants confer risk of a range of psychiatric disorders, including ADHD and BD (Smoller et al., 2013). As molecular genetic research of ADHD and BD is not a central part of this thesis, it is not reviewed in more detail here. Importantly, common genetic risk factors influence susceptibility to both ADHD and BD (Smoller et al., 2013).

Current diagnostic criteria aim to discriminate between disorders such as ADHD and BD based on distinct clusters of signs and symptoms, which are predictive of clinical parameters including course, outcome and treatment response (Farmer, McGuffin, & Williams, 2002). Yet, differentiation between ADHD and BD may be complicated by their symptom overlap. A diagnosis of mania, based on DSM-IV criteria, requires the presence of elevated, expansive or irritable mood for a week or more, as well as several secondary features including decreased need for sleep, distractibility, psychomotor agitation and increased talkativeness. Several of these symptoms, particularly distractibility (or inattention), motor restlessness (or hyperactivity) and talkativeness, are also central to the diagnosis of ADHD in the DSM-IV (American Psychiatric Association, 2000; Asherson et al., 2014; Kent & Craddock, 2003; Klassen et al., 2010). Beyond core diagnostic features of DSM-IV, ADHD and BD also overlap on symptoms of mood dysregulation such as irritability and emotional lability in ADHD, which match the symptoms of mood fluctuation in BD

(Asherson et al., 2014; Chan, Stringaris, & Ford, 2011; Skirrow & Asherson, 2013; Skirrow, Hosang, Farmer, & Asherson, 2012). The introduction of the DSM-5 has further complicated the picture, as mood dysregulation is now acknowledged as an associated feature of ADHD, and “persistently increased goal-directed activity or energy” is recognised as a symptom of BD (American Psychiatric Association, 2013).

Clinical challenges, for example in establishing the most appropriate treatment, may arise from problems in delineating the two disorders and recognising comorbidities, owing to the symptom overlap (Asherson et al., 2014). Whereas psychostimulants or atomoxetine are employed in the treatment of ADHD, mood stabilisers or antipsychotics are used to treat mania. Research suggests that incorrect treatment may result in non-response or aggravation of symptoms, particularly in BD (Asherson et al., 2014; DelBello et al., 2001; Klassen et al., 2010; Scheffer, 2007). Consequently, for optimal outcome and treatment response, the presentation of symptoms requires careful deliberation, but key differences in symptomatology may help to delineate ADHD and BD.

#### *1.6.1.3 Delineation from ADHD*

One crucial distinction between ADHD and BD is the time-course of symptom presentations. While BD presents with distinct and recurrent episodes of mood disturbances, ADHD symptoms show persistent trait-like qualities (American Psychiatric Association, 2000, 2013; Asherson et al., 2014; Skirrow et al., 2012; van Schalkwyk & Schronen, 2010; Wilens et al., 2003). Importantly, the persistent trait-like ADHD symptoms reflect deviations from developmental norms, whereas the episodic BD symptoms are thought of as changes from an individual's idiosyncratic premorbid state (Skirrow et al., 2012). Yet, DSM-IV criteria for BD allow for considerable heterogeneity in the time-course of symptom presentations. While BD-I and BD-II are characterised by a strict episodic nature with clear euthymic periods, cyclothymia represents a more chronic form of BD (Skirrow et al., 2012).

In addition, several symptoms that are commonly observed during manic (i.e. elation, decreased need for sleep and grandiosity) and depressive episodes

(i.e. psychomotor retardation, fatigue or loss of energy, hypersomnia, loss of interest in pleasure and thoughts of death and suicidality) in individuals with BD are not part of the ADHD diagnosis (Asherson et al., 2014). Subtle differences further exist in the overlapping symptoms. The low mood exhibited by some individuals with ADHD, for example, may stem from low self-esteem and low self-confidence due to frustration with poor achievement in academic, vocational or social relationships, rather than reflecting a comorbid depressive disorder (Scheffer, 2007). Moreover, while individuals with ADHD frequently experience incessant mind wandering (everyday and task-unrelated thoughts flitting from one topic to another), individuals with BD may perceive their thoughts as 'racing' and as being particularly sharp (Asherson, 2005).

Delineating between ADHD and BD, thus, requires careful clinical consideration. Few studies have directly investigated the suitability of standard clinical measures to differentiate between ADHD and BD. One study that compared individuals with ADHD (n=16) to individuals with BD (n=15) on a depression scale found that both clinical groups had elevated scores compared to controls (Torralva et al., 2011). Another study demonstrated that while ADHD measures successfully distinguished ADHD from BD, the ADHD group (n=12) showed higher depression and manic symptoms than euthymic BD participants (n=13) (Ibanez et al., 2012). However, no firm conclusions can be drawn from these studies due to small sample sizes and the use of self-report measures. Consequently, the degree of overlap and separation between ADHD and BD remain to be elucidated directly in cross-disorder comparison studies.

### ***1.6.2 Cognitive-neurophysiological impairments***

Individuals with BD experience cognitive impairments across multiple domains such as working memory, sustained attention and processing speed (Bora, Yücel, & Pantelis, 2010; Bourne et al., 2013; Daban et al., 2012; Kurtz & Gerraty, 2009; Latalova, Prasko, Diveky, & Velartova, 2011; Lee et al., 2014; Quraishi & Frangou, 2002; Robinson et al., 2006). A meta-analysis, which reviewed 42 studies of 1,197 euthymic individuals, 13 studies of 314 individuals in a manic/mixed phase of BD and 5 studies of 96 individuals in a depressed state, reported impairments in sustained attention, working memory and other

EFs of moderate-to-large effect in euthymic (Cohen's  $d=0.61-0.83$ ), manic/mixed ( $d=0.64-1.43$ ), as well as depressive episodes ( $d=0.55-1.31$ ) (Kurtz & Gerraty, 2009). These findings suggest that the cognitive impairments associated with BD are state-independent. Indeed, deficits in EF have been reported in individuals prior to the onset of BD in two prospective longitudinal studies (Meyer et al., 2004; Ratheesh et al., 2013). Premorbid IQ, however, has been found to be comparable to that of healthy controls (Martino, Samamé, Ibañez, & Strejilevich, 2015; Reichenberg et al., 2002; Sørensen, Sæbye, Urfer-Parnas, Mortensen, & Parnas, 2012; Zammit et al., 2004).

Several cognitive impairments, particularly impairments in EF, have also been found in first-degree relatives of individuals with BD such as parents, sibling and children (Adleman et al., 2014; Arslan, Tiryaki, & Ozkorumak, 2014; Arts, Jabben, Krabbendam, & van Os, 2008; Bora, Yucel, & Pantelis, 2009; Brotman, Rooney, Skup, Pine, & Leibenluft, 2009; Erol, Kosger, Putgul, & Ersoy, 2013; Ethridge et al., 2014; Ferrier, Chowdhury, Thompson, Watson, & Young, 2004; Kulkarni, Jain, Janardhan Reddy, Kumar, & Kandavel, 2010; Pattanayak, Sagar, & Mehta, 2012; Robinson et al., 2006; Schulze et al., 2011), indicating familial influences on these neurocognitive deficits.

Neurophysiological deficits associated with BD have been investigated using QEEG and ERPs. Three reviews of QEEG studies in BD concluded that individuals with BD show atypical oscillation patterns during resting-state conditions, reflected by elevated theta and delta activity, as well decreased alpha power (Başar & Güntekin, 2013; Degabriele & Lagopoulos, 2009; Outhred, Kemp, & Malhi, 2014). ERP studies of individuals with BD have frequently reported abnormalities in P3 components (Bersani et al., 2015; Bestelmeyer, 2012; Bestelmeyer, Phillips, Crombie, Philip Benson, & St.Clair, 2009; Degabriele & Lagopoulos, 2009), adding to existing evidence of attention deficits in BD (Bora et al., 2010; Bourne et al., 2013; Daban et al., 2012; Kurtz & Gerraty, 2009; Latalova et al., 2011; Lee et al., 2014; Quraishi & Frangou, 2002; Robinson et al., 2006). A lower P3 amplitude and a longer P3 latency has also been found in relatives of individuals with BD (Hall et al., 2007; Pierson, Jouvent, Quintin, Perez-Diaz, & Leboyer, 2000), suggesting familial influences on this ERP component. Few studies of individuals with BD have investigated

the ERP components ERN and N2, which are thought to reflect conflict monitoring. One study showed a significantly reduced N2 amplitude in participants with BD, reflecting reduced conflict monitoring, compared to control groups in response to NoGo stimuli during a cued CPT (Michelini et al., 2015).

#### *1.6.2.1 Comparison with ADHD*

Similar cognitive impairments have been described in ADHD and BD. Both individuals with ADHD and individuals with BD show deficits in EF, such as attentional and inhibitory processes (Arts et al., 2008; McLoughlin et al., 2010; Robinson & Ferrier, 2006; Torralva et al., 2011). In addition, increased RTV, reflecting short-term fluctuations in attentional performance, has been reported for individuals with ADHD, individuals with BD as well as their first-degree relatives (Adleman et al., 2014; Brotman et al., 2009; Kuntsi & Klein, 2012; Kuntsi et al., 2010).

Despite these similarities, few studies have directly compared ADHD and BD samples on cognitive and neurophysiological measures to examine the mechanisms underlying these impairments (Skirrow et al., 2012). One direct comparison study, and one review of cognitive deficits in ADHD and BD separately, concluded that subtle differences in the EF deficits associated with ADHD and BD may aid in the differentiation between the disorders (Torralva et al., 2011; Walshaw, Alloy, & Sabb, 2010).

Direct comparisons of neurophysiological impairments associated with ADHD and BD are scarce and limited by small sample sizes. One study examining decision-making and reward-related processes of the brain in adults with ADHD (n=12), BD (n=13) and controls (n=25) using a gambling task demonstrated impairments in the feedback-related negativity (FRN) in both the BD and ADHD groups compared to controls (Ibanez et al., 2012). Like controls, individuals with BD displayed an increasing P3 component relative to increasing reward magnitude. Individuals with ADHD, instead, demonstrated no modulation of P3 response in response to reward magnitude changes. Another study investigated early cortical processing of emotional stimuli in adults with ADHD (n=16), BD (n=14) and schizophrenia (n=15), as well as in the unaffected relatives of

schizophrenia participants (n=14) and controls (n=41), using a face-word valence task (Ibanez et al., 2014). A shared impairment in the N170 components, indicating emotional face processing, was found in the clinical groups. While individuals with BD demonstrated additional abnormal emotional processing of semantic information, individuals with ADHD showed a specific impairment in the processing of simultaneous emotional stimuli. A direct comparison of women with ADHD (n=20), euthymic BD (n=20) and controls (n=20) on a cued CPT found an attenuation of NoGo-P3 amplitude (inhibitory control) in the clinical groups compared to controls. In addition, the BD group demonstrated reduced NoGo-N2 amplitude (conflict monitoring) compared to both ADHD and control groups. According to the authors, these findings may suggest disorder-specific (conflict monitoring) and overlapping (inhibitory control) neurophysiological impairments in women with ADHD and women with BD (Michelini et al., 2015).

Furthermore, to assess brain functional connectivity and variability in adults with ADHD (n=9) and euthymic BD (n=11) relative to healthy controls (n=15), another study employed a graph theory approach (Barttfeld et al., 2014). Increased functional connectivity was observed in the ADHD and BD groups. Yet, individuals with ADHD showed enhanced variability compared to controls, while in individuals with BD variability was reduced. Lastly, one study assessed mathematical approaches intended to classify groups of patients with ADHD and BD on the basis of EEG using data from adults with ADHD (n=21) or BD (n=22) (Sadatnezhad, Boostani, & Ghanizadeh, 2011). EEG data from eyes-open and eyes-closed resting-state conditions allowed a high classification rate between individuals with ADHD and BD with 78-86% specificity, depending on the exact method used. As the purpose of the paper was the examination of mathematical approaches to improve classification and diagnosis, no EEG parameter differences between the groups are reported. While limited in number, direct comparisons of ADHD and BD have furthered our understanding of the neurophysiology underlying these disorders, indicating both disorder-specific and shared neurophysiological impairments in individuals with ADHD and BD. Yet, more research is needed to gain greater insight into cross-disorder differences and similarities.

### ***1.6.3 Summary***

BD is a chronic affective disorder characterised by recurrent episodes of mania (or hypomania) and depression. Both males and females are equally affected by BD, although differences in its expression (e.g. comorbidities and BD type) may exist. Because of its heterogeneous nature, BD is best conceptualised as a spectrum. Cognitive and neurophysiological impairments in BD can be severe and commonly persist during periods of euthymia. Research into these impairments has mainly focused on a few deficits, such as EF and the P3 ERP component. The diagnostic criteria for BD include symptoms that overlap with ADHD, which may result in clinical challenges regarding treatment and management plans when the disorder is severe and presents with mental health symptoms such as restlessness, emotional instability, low self-esteem, and sleep problems (Asherson et al., 2014). As careful clinical consideration is required to delineate between ADHD and BD, some direct comparisons have tried to elucidate the biological mechanisms underlying these disorders. Overall, research of cognitive and neurophysiological impairments suggests both shared and unique deficits in ADHD and BD. However, for firm conclusions on the nature of the neurophysiological deficits in ADHD and BD and the extent to which they overlap or dissociate more research is needed.

## **1.7 Preterm birth**

Preterm birth has been associated with an increased risk for ADHD-like symptoms and cognitive impairments. Whether these reflect identical behavioural symptoms and cognitive–neurophysiological impairments in term-born individuals with ADHD is unclear. Direct comparisons of individuals born preterm and individuals with ADHD on cognitive-neurophysiological measures may inform us on potential biomarkers and may guide more effective, targeted interventions.

### ***1.7.1 Epidemiology***

Preterm birth denotes all births before 37 completed weeks of gestation (World Health Organization, 1977). Based on data from 184 countries, the worldwide prevalence of preterm birth is estimated at 11.1%, ranging from 8.6% in



developed countries and Latin America to 13.3% in Southeastern Asia (Blencowe et al., 2012). Approximately 5% of preterm births are extremely preterm (<28 weeks), about 15% are very preterm (28 to <32 weeks), roughly 20% moderately preterm (32 to <34), and 60–70% are late preterm births (34 to <37 completed weeks of gestation) (Goldenberg, Culhane, Iams, & Romero, 2008).

Preterm birth may result from an induction of labour (or elective caesarean birth) for medical reasons or from spontaneous labour onset owing to a range of risk factors. Risk factors include genetic influences, extreme maternal reproductive ages (<18 or >40), lifestyle factors (obesity, tobacco, alcohol and drug use), infections or allergic reactions, and psychosocial stresses (Goldenberg et al., 2008; Muglia & Katz, 2010; Plunkett & Muglia, 2008; Wu et al., 2015). Many of these risk factors result in DNA methylation changes (e.g. Maccani, Koestler, Houseman, Marsit, & Kelsey, 2013; McKay, Waltham, Williams, & Mathers, 2011; Oberlander et al., 2008). As studies have reported an association of DNA methylation and other epigenetic differences with gestational age (GA) and growth patterns (Novakovic et al., 2011; Schroeder et al., 2011; Tobi et al., 2011), epigenetic processes have been proposed as a potential mechanism contributing to preterm birth and its long-term effects (Parets, Bedient, Menon, & Smith, 2014).

Preterm birth is linked to numerous adverse long-term effects, such as increased risk of mortality during infancy (D'Onofrio et al., 2013; Fellman et al., 2009; Moster, Lie, & Markestad, 2008; Patel et al., 2015) and young adulthood (Crump, Sundquist, Sundquist, & Winkleby, 2011), as well as morbidity across the lifespan (Doyle & Anderson, 2010; McCormick, Litt, Smith, & Zupancic, 2011). Morbidity associated with preterm birth includes psychiatric disorders (D'Onofrio et al., 2013; Samantha Johnson & Marlow, 2014; Moster et al., 2008; Treyvaud et al., 2013), academic problems (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; D'Onofrio et al., 2013; Lindström, Lindblad, & Hjern, 2011; McGowan, Alderdice, Holmes, & Johnston, 2011; Moster et al., 2008), and social challenges, such as higher levels of unemployment and criminal activity,

as well as lower income (D'Onofrio et al., 2013; Lindström, Winblad, Haglund, & Hjern, 2007; Männistö et al., 2015; Moster et al., 2008; Saigal et al., 2009).

A recent large-scale population-based cohort study of all individuals born in Sweden between 1973 and 2008 ( $n=3,300,708$  offspring of 1,736,735 mothers) investigated the relationship of preterm birth with offspring mortality and morbidity using a quasi-experimental design (D'Onofrio et al., 2013). The study found strong associations between GA and risk of infant mortality in preterm-born compared to term-born individuals, with hazard ratios (HRs) ranging from 288.1 for individuals born 23–27 weeks of gestation to 6.9 in individuals born 34–36 weeks of gestation. In line with a causal effect, GA significantly predicted infant mortality within discordant sibling pairs across the entire range of GA while controlling for familiarity. Extremely preterm GA (<28 weeks) was also linked to increased risk of psychiatric disorders, such as psychotic or bipolar disorders ( $HR=3.2$ ), autism ( $HR=3.2$ ), and ADHD ( $HR=2.3$ ), as well as lower educational attainment ( $HR=1.7$ ). While the magnitude of the association between psychiatric disorders and GA was only slightly attenuated within sibling pairs, suggesting that familial confounder account for a very small proportion of the increased risk of psychiatric conditions with shorter GA, the magnitude of the association between educational attainment and GA was greatly attenuated within sibling pairs, suggesting that confounding factors shared by siblings account for a large proportion of the association. These findings are in line with a causal explanation for the association between preterm birth and the increased risk of psychiatric disorders.

Preterm birth can have adverse effects on cognitive and neurophysiological development. A systematic review of long-term outcomes of intrauterine and neonatal insults concluded that, worldwide, the most common impairments in preterm-born individuals were learning difficulties, cognitive deficits and developmental delay, impacting 60% of those born preterm (Mwaniki, Atieno, Lawn, & Newton, 2012). The cognitive and neurophysiological impairments associated with preterm birth are reviewed below (see section 1.7.2).

### *1.7.1.1 Gender differences*

Compared to females, males are at somewhat greater risk of preterm birth, with about 55% of preterm births being males (Blencowe et al., 2013; Ingemarsson, 2003; Kent, Wright, & Abdel-Latif, 2012; Vatten & Skjaerven, 2004; Zeitlin, 2002; Zeitlin, Ancel, Larroque, & Kaminski, 2004). More postnatal complications, higher overall perinatal mortality rates and poorer long-term outcome are also seen in preterm males compared to females born at similar gestation (Brothwood, Wolke, Gamsu, Benson, & Cooper, 1986; Costeloe, Hennessy, Gibson, Marlow, & Wilkinson, 2000; Hack & Fanaroff, 2000; Ingemarsson, 2003; Kent et al., 2012; Peacock, Marston, Marlow, Calvert, & Greenough, 2012; Roy, Kumar, Kaur, & Faridi, 2014; Smith, 2000; Stevenson et al., 2000; Verloove-Vanhorick et al., 1994). Moreover, a male disadvantage has been reported for long-term neurodevelopmental outcome (Hintz, Kendrick, Vohr, Kenneth Poole, & Higgins, 2006; Månsson, Fellman, & Stjernqvist, 2015; Peacock et al., 2012).

Yet, the underlying mechanisms for these gender differences remain unclear. The mechanisms proposed to underlie the higher prevalence of preterm-born males include heavier average body weight, which may increase the probability of preterm labour (Hall & Carr-Hill, 1982; McGregor, Leff, Orleans, & Baron, 1992), a greater susceptibility to particular medical complications linked to preterm birth, such as pregnancy-induced hypertension or infection (Campbell, MacGillivray, Carr-Hill, & Samphier, 1983; MacGillivray & Davey, 1985), and sex-linked biochemical processes (Cooperstock & Campbell, 1996). Worse long-term outcomes may be explained by the relative immaturity of preterm-born males compared to females born at similar gestation (Peacock et al., 2012).

### *1.7.1.2 ADHD and preterm birth*

One frequently reported psychiatric outcome of preterm birth is ADHD. A meta-analysis of studies conducted between 1980 and 2001 demonstrated that school-aged children ( $\geq 5$  years) born preterm ( $n=1,556$ ) were at heightened risk ( $RR=2.64$ ) of developing ADHD relative to controls ( $n=1,720$ ) (Bhutta et al., 2002). In a population-based sample of children born extremely preterm ( $<26$

weeks), the risk of ADHD was further increased by over four-fold (odds ratio; OR=4.2) (Johnson et al., 2010). In line with these findings, a Swedish register study of 1,180,616 children born between 1987 and 2000 reported a stepwise increase in ORs for ADHD medication with increasing degree of immaturity at birth, ranging from 2.1 for extremely preterm (23 to 28 weeks) to 1.3 for late preterm (35 to 36 weeks) (Lindström et al., 2011). In term-born children, being small for GA also increased the risk of ADHD medication by 1.4. However, being small for GA did not modify the effect of GA on ADHD medication, suggesting that different mechanisms may underlie the associations. Furthermore, familial factors were unlikely to account for the effect, as ORs for risk of ADHD were highly similar across GA in a within-mother-between-pregnancy analysis (Lindström et al., 2011). The finding that risk of ADHD increases independently of shared familial confounders was confirmed in a population-based cohort study of all individuals born in Sweden between 1973 and 2008 (n=3,300,708 offspring of 1,736,735 mothers) (D'Onofrio et al., 2013).

The long-term effects of preterm birth, including heightened risk of ADHD, have also been found to persist into adulthood. A population-based study of Norwegian adults reported a 1.3 and 5-fold increased risk for ADHD in adults born preterm (<37 weeks) and extremely preterm (<28 weeks), respectively, persisting at least 40 years after birth (Halmøy, Klungsøyr, Skjærven, & Haavik, 2012). Preterm research investigating ADHD symptoms as a continuum (for a discussion see section 1.1.1) demonstrates a similar pattern of findings. A meta-analysis reported significantly more attention problems among children born very preterm (<32 weeks) and/or with a very low birth weight (<1,500g) (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). Teacher- and parent-ratings of attention problems were found to be 0.43 to 0.59 standard deviations (SD) higher in very preterm and/or very low birth weight children (n=4,125) compared to controls (n=3,197).

In addition, a longitudinal study of more than 14,000 twins registered in the Netherlands Twin Register found that birth weight was negatively associated with attention problems (Pettersson et al., 2015). Children in the lowest birth weight category of 1,500 to 2,000 g scored 0.18 to 0.37 SD higher on ratings of attention problems than children in the reference category of 3,000 to 3,500 g.

These findings were supported by a longitudinal cohort study of all twins born in Sweden between 1992 and 2000 ( $n=21,775$ ) which demonstrated that a reduction of one kilogram of birth weight corresponded to parents rating their child nearly one unit higher on the total ADHD scale ( $\beta=-0.42$ ), even after controlling for all environmental and genetic confounds shared within twin pairs (Pettersson et al., 2015). In support of these findings and in line with a causal effect of birth weight on attention problems, one study reported that in discordant twins the lighter-born twin scored higher on attention problems (Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011). More support for a causal effect of birth weight on attention problems comes from a population-based sibling sample ( $n=1,266$ ), which was followed up over 14 years: the effect of birth weight and being small for GA on ADHD symptoms was shown in term-born and preterm-born individuals (Groen-Blokhuis et al., 2011; Lindström et al., 2011). One longitudinal cohort study of individuals born between 1985 and 1986 ( $n=828$ ) in Finland even found that instead of GA, lower birth weight and being small for GA only were associated with higher ADHD symptom scores (Heinonen et al., 2010). However, overall, the relative importance of birth weight versus GA in the association with ADHD diagnosis and symptoms remains unclear. While research has provided strong support for the link between preterm birth (and/or low birth weight) and ADHD, little is known about the underlying risk pathways. Neurophysiological assessments have the potential to elucidate these pathways further.

### ***1.7.2 Cognitive-neurophysiological impairments***

Preterm-born individuals are at increased risk of cognitive impairments in areas such as memory performance, academic achievement and attention across the lifespan. Impairments in all memory domains have been reported in children born preterm (Anderson, 2014; Omizzolo et al., 2014). Yet, most studies have focused on working memory (Anderson, 2014). Preterm samples have demonstrated deficits in both verbal (Aarnoudse-Moens et al., 2009; Anderson & Doyle, 2004; Hutchinson, De Luca, Doyle, Roberts, & Anderson, 2013) and visual working memory tasks (Baron, Erickson, Ahronovich, Litman, & Brandt, 2010; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Rose, Feldman, Jankowski, & Van Rossem, 2011), compared to term-born controls. Both cross-

sectional and follow-up studies suggest that working memory impairments in children born preterm decrease with age (Curtis, Lindeke, Georgieff, & Nelson, 2002; Rushe et al., 2001; Saavalainen et al., 2007).

Poor academic achievement has also been associated with preterm birth (Anderson & Doyle, 2003; Hutchinson et al., 2013; Johnson et al., 2009; Litt et al., 2012), with shorter GA predicting greater academic underachievement (Aarnoudse-Moens et al., 2009; Johnson et al., 2009; Taylor, Espy, & Anderson, 2009). A meta-analysis of 14 studies on academic achievement found that very preterm ( $\leq 33$  weeks) or very low birth weight ( $\leq 1500$ g) children scored 0.60 SD lower on mathematics tests, 0.48 SD lower on reading tests, and 0.76 SD lower on spelling tests than term-born controls (Aarnoudse-Moens et al., 2009). An association between preterm birth and lower mean IQ scores has also consistently been reported. A recent meta-analysis of all studies ( $N=27$ ) conducted between 1980 and 2009 found that individuals born preterm ( $n=3,504$ ) scored an average of 11.94 IQ points lower than term-born individuals ( $n=3,540$ ). In addition, there was a strong negative association between GA and IQ ( $r=-0.88$ ,  $p=0.001$ ) (Kerr-Wilson, Mackay, Smith, & Pell, 2012). Yet, it is unclear how these general cognitive impairments relate to the other cognitive deficits (Lee, Yeatman, Luna, & Feldman, 2011; Loe, Lee, Luna, & Feldman, 2012).

Numerous studies have examined attention problems in individuals born preterm (van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008). A meta-analysis of selective and sustained attention in preterm-born children demonstrated poorer performance in preterm-born children ( $n=1,196$ ) compared to term-born controls ( $n=1,008$ ) on selective attention tasks, with a moderate effect size of Cohen's  $d=0.38$ . A systematic review also reported poorer sustained attention in preterm-born children ( $n=885$ ) compared to term-born controls ( $n=802$ ), with a moderate effect size of Cohen's  $d=0.45$  (Mulder, Pitchford, Hagger, & Marlow, 2009). These findings were confirmed by two cohort studies investigating attention in 189 children and 228 adolescents born extremely preterm ( $<28$  weeks) or extremely low birth weight ( $<1,000$ g), compared to 173 term-born children and 166 term-born adolescents respectively (Anderson et al., 2011; Wilson-Ching et al., 2013).

Compared to term-born controls, children born preterm were 2.4 times more likely to show deficits in selective and sustained attention, and more than three times more likely to show deficits in shifting and divided attention (Anderson et al., 2011). Adolescents born preterm were 2.5 more likely to display deficits in selective, shifting and divided attention, but performed similar to term-born controls on sustained attention tasks (Wilson-Ching et al., 2013).

In addition, two meta-analyses have investigated EF in children born preterm (Aarnoudse-Moens et al., 2009; Mulder et al., 2009). The first meta-analysis focussed on response inhibition in Go/NoGo tasks, verbal fluency, planning ability, and set shifting in studies of preterm-born children published between 1990 and 2008. Eight studies of response inhibition, pooling the results of 830 preterm-born and 740 term-born children, were included in the meta-analysis. These studies yielded a small-to-moderate effect size (Cohen's  $d=0.25$ ) and a significant positive correlation between GA and response inhibition ( $R^2=0.74$ ), suggesting that response inhibition is impaired in children born preterm. Verbal fluency, planning ability and set shifting were also found to be impaired in individuals born preterm, with effect sizes ranging from 0.38 to 0.50 (Mulder et al., 2009). The second meta-analysis included studies published between 1998 and 2008 and investigating verbal fluency, working memory and cognitive flexibility in very preterm ( $\leq 33$  weeks) and very low birth weight ( $\leq 1500$ g) children. Preterm-born children scored 0.57 SD lower for verbal fluency, 0.36 SD lower for working memory, and 0.49 SD lower for cognitive flexibility compared to term-born controls (Aarnoudse-Moens et al., 2009). Taken together, these meta-analyses suggest preterm-born children are at increased risk of poorer EF. Impairments in EF have also been found in adolescents (Burnett et al., 2015; Taylor, Minich, Bangert, Filipek, & Hack, 2004) and adults born preterm (Nosarti et al., 2007; Stålnacke, Lundequist, Böhm, Forssberg, & Smedler, 2014), indicating that these impairments may persist across the lifespan.

Atypical brain maturation, which has been reported in very preterm children (Miller & Ferriero, 2009), may be related to the cognitive impairments seen in individuals born preterm. Most studies investigating the neurophysiology of individuals born preterm have used functional magnetic resonance imaging

(fMRI) or magnetoencephalography (MEG). Studies employing fMRI have demonstrated reduced activation (as measured by the Blood Oxygen Level Dependent (BOLD) contrast) in preterm-born children, compared to term-born controls during cognitive task performance (Damaraju et al., 2010; Griffiths et al., 2013; Silja Torvik Griffiths et al., 2013, 2014; Lawrence et al., 2009; Ment et al., 2006; Nosarti et al., 2006; Peterson et al., 2002; Schafer et al., 2009). In addition, MEG studies have revealed altered cortical responses in preterm-born neonates (Nevalainen et al., 2008), altered cortical activation and inter-regional connectivity in preterm-born children and adolescents (Boersma et al., 2013; Doesburg et al., 2011; Frye et al., 2009, 2010; Moiseev, Doesburg, Herdman, Ribary, & Grunau, 2014). Moreover, MEG research demonstrated atypical oscillatory patterns in children born very preterm (Doesburg et al., 2011), which were linked to worse neonatal experience and childhood outcome (Doesburg et al., 2013).

While several EEG studies have examined the neurophysiology of preterm-born infants in neonatal intensive care units (Meijer et al., 2014; Victor, Appleton, Beirne, Marson, & Weindling, 2005) or in the postnatal period (Beckwith & Parmelee, 1986; Duffy, Als, & McAnulty, 1990; González et al., 2011; Hayakawa et al., 2001; Vecchierini, André, & D'Allest, 2007), less EEG research has been conducted in children, adolescents or adults born preterm. One study that investigated EEG spectral power in individuals born preterm during an eyes-closed resting condition reported increased theta (3.6– 5 Hz), beta (20.1–30 Hz) and gamma (30.1– 40.2 Hz) power in preterm-born school-aged children with educational problems (n=38), compared to term-born controls with educational problems (n=22) (Rozhkova, 2008). Furthermore, non-impaired (defined as being free of neurosensory impairments and psychiatric disorders) young adults born at extremely low birth weight (n=71) showed increased power in the slow (delta and theta) and decreased power in the fast (alpha and beta) frequency bands (Miskovic, Schmidt, Boyle, & Saigal, 2009), as well as greater relative right frontal EEG activity at rest (Schmidt, Miskovic, Boyle, & Saigal, 2010), compared to controls born at healthy birth weight (n=83). The discrepancies between the studies may be explained by differences in sample characteristics, such as sample size, age, GA and birth weight.



Attenuated P1, potentially reflecting impaired primary auditory processing, and larger N2 amplitudes, possibly indicating impaired attention orienting, have been found in 5-year-old children born very preterm (<32 weeks) performing on an auditory oddball task (Hövel et al., 2014; Mikkola et al., 2007). These findings of increased N2 amplitude are comparable to ERP abnormalities reported in studies of children with neurodevelopmental disorders such as dyslexia, autism and ADHD (Albrecht et al., 2008; Gow et al., 2012; Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009; McLoughlin et al., 2009).

#### *1.7.2.1 Comparison with ADHD*

While the cognitive and neurophysiological processes impaired in individuals born preterm appear similar to those implicated in ADHD, including attention and inhibitory control difficulties (Aarnoudse-Moens et al., 2009; Geva & Feldman, 2008; Lawrence et al., 2009; Miskovic et al., 2009; Mulder et al., 2009; Nosarti et al., 2006), only one ERP study to date has directly compared these two populations. The ERP study included very low birth weight children born preterm (<1501g and <34 weeks) with (n=9) and without ADHD (n=10), as well as term-born controls (n=12) and term-born individuals with ADHD (n=10) (Potgieter, Vervisch, & Lagae, 2003). The study found that children with ADHD, independent of whether they were born preterm or full term, displayed abnormalities in certain ERP markers that are sensitive to deficits in ADHD, most notably the NoGo-N2 indexing response inhibition. However, the sample size was very small and the test battery restricted to a visual oddball task. Consequently, these findings require replication. For more effective, targeted interventions, the study of preterm birth should include direct comparisons with individuals with ADHD to establish whether the deficits seen in individuals born preterm are identical to those associated with ADHD or part of more wide-ranging impairments.

#### **1.7.3 Summary**

Preterm birth, which is defined as birth before 37 completed weeks of gestation, is highly prevalent worldwide, with males at greater risk of being born preterm than females. The survival rates for individuals born preterm have increased

greatly over the last decade (Goldenberg et al., 2008). While most organs are immature following preterm birth, the brain is particularly susceptible to the consequences of preterm birth (Rees & Inder, 2005). As a result, preterm-born individuals are at increased risk of adverse long-term outcomes compared to their term-born counterparts, especially with regards to psychiatric morbidity and cognitive-neurophysiological impairments. One of the most consistently reported psychiatric outcomes of preterm birth is ADHD, whether ADHD is considered as a continuum or a categorical diagnosis. Furthermore, the cognitive and neurophysiological domains commonly impaired in individuals born preterm including IQ, attention, EF and increased theta power are those also implicated in ADHD. Yet, few studies have directly compared individuals born preterm to individuals with ADHD. More research is needed to understand whether the ADHD-like symptoms reported among individuals born preterm reflect ADHD in term-born individuals, with identical cognitive–neurophysiological impairments. A better understanding of the differences and commonalities in the impairments of individuals born preterm and individuals with ADHD will enable more effective, targeted interventions.

## **1.8 Aims and objectives**

In this thesis, ADHD is investigated in the context of associated conditions, as well as risk and protective factors. Using a combination of cognitive-neurophysiological and genetically-sensitive longitudinal designs, this thesis aims to elucidate neurophysiological processes underlying ADHD and related conditions, and the mechanisms that contribute to the risk of and protection from ADHD.

### ***1.8.1 Chapters 2, 3 and 4***

The first three data-based chapters examine the association of ADHD with bipolar disorder (BD) and preterm birth. The aim of chapter 2 is to examine quantitative EEG differences and similarities between women with ADHD, women with BD and healthy controls during a resting-state (EO) and a cognitive task (CPT-OX) condition and to explore how cortical activity patterns change in relation to recording condition (rest vs. cognitive task condition) in the three

groups. This chapter, therefore, aims to further our understanding of potentially overlapping and distinct neurophysiological impairments that bring about the symptomatic overlap in ADHD and BD. The ultimate aim of this analysis is to identify biomarkers, which may aid clinical differentiation of these disorders, and may improve disorder management.

Chapter 3 aims to investigate the commonalities and differences in brain function between ADHD and preterm birth using quantitative EEG in adolescents born preterm, term-born adolescents with ADHD and term-born controls during a resting-state condition (eyes open, EO) and a cognitive task condition (a cued CPT with flankers, CPT-OX). Similar to chapter 2, this analysis investigates the change in cortical activation patterns arising from the transition from resting-state to cognitive task condition. Chapter 4 intends to elucidate whether the ADHD-like symptoms and cognitive impairments in individuals born preterm reflect identical cognitive–neurophysiological impairments in term-born individuals with ADHD by directly comparing preterm born adolescents, term-born adolescents with ADHD and term-born controls on cognitive-performance and ERP measures obtained from a CPT-OX. In addition, chapters 3 and 4 aim to examine the relationship of age with EEG spectral power and ERP components respectively in adolescents born preterm, term-born adolescents with ADHD and term-born controls. Ultimately, the purpose of these two studies is to guide future interventions aimed at individuals born preterm by informing us on neurophysiological impairments that are shared between preterm-born individuals and individuals with ADHD and that, therefore, may underlie cognitive and symptomatic similarities.

### ***1.8.2 Chapters 5 and 6***

The remaining two data-based chapters employ genetically-sensitive designs to examine risk and protective factors associated with ADHD. The first aim of chapter 5 is to establish the developmental pattern of the association of ADHD symptoms with verbal IQ (VIQ) and performance IQ (PIQ) in a population-based twin sample. While ADHD symptoms typically diminish in severity over the course of puberty (~ages 12–16 years (Willcutt, 2012)), individuals with high levels of ADHD symptoms are at increased risk of continuing problems related

to ADHD during adolescence (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011; Rasmussen & Gillberg, 2000). We are, therefore, interested in the developmental pattern of the association of ADHD symptoms with VIQ and PIQ at ages 12, 14 and 16 years; a period of rapid developmental change for which both ADHD and IQ data are available in our large twin sample. The second aim of this study is to examine the genetic and environmental aetiologies of the association of ADHD symptoms with VIQ and PIQ within time point, and their stability across time. Making use of the inherently time-ordered nature and genetic sensitivity of the data, we use a cross-lagged model to address these two objectives: namely, we establish the direction of effects, while modelling the genetic and environmental variance and covariance structure of the data separately for VIQ and PIQ.

The final chapter (chapter 6) aims to examine the effect of physical activity (PA) during late adolescence on ADHD symptoms in early adulthood. Both the symptoms and functional impairments associated with ADHD often persist across the lifespan (Faraone et al., 2006). The effect of PA on ADHD symptoms is investigated together and separately for the two sub-components of ADHD, inattention and hyperactivity-impulsivity. Investigating the effect in 232 MZ twin pairs enables us to control for unmeasured genetic and shared environmental confounding factors that may influence the relationship between PA and ADHD symptoms, allowing us to draw tentative causal inferences about this relationship. This study, ultimately, aims to provide support for a novel non-pharmacological treatment or management strategy for ADHD on the basis of our growing understanding of the potential protective factor PA.

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## Chapter 2. Commonalities in EEG spectral power abnormalities between ADHD and bipolar disorder during rest and cognitive performance

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### 2.1 Abstract

**Background:** While attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) denote distinct psychiatric conditions, diagnostic delineation is impeded by considerable symptomatic overlap. Direct comparisons across ADHD and BD on neurophysiological measures are limited, but could inform us on impairments that are specific to or shared between the disorders and, therefore, potential biomarkers that may aid clinical differentiation of these disorders. The aim of this study was to test whether quantitative EEG (QEEG) identifies differences or similarities between women with ADHD and women with BD during resting-state and task conditions. **Methods:** QEEG activity was directly compared between 20 ADHD, 20 BD and 20 control women during an eyes-open resting-state condition (EO) and a cued continuous performance task (CPT-OX). **Results:** Both ADHD ( $t=2.50$ ,  $df=38$ ,  $p=0.017$ ) and BD ( $t=2.54$ ,  $df=38$ ,  $p=0.018$ ) participants showed higher theta power during EO than controls. No significant differences emerged between the two clinical groups. While control participants showed a task-related increase in theta power from EO to CPT-OX ( $t=-3.77$ ,  $df=19$ ,  $p=0.001$ ), no such change in theta power was observed in the ADHD ( $t=-0.61$ ,  $df=19$ ,  $p=0.553$ ) or BD ( $t=1.82$ ,  $df=19$ ,  $p=0.084$ ) groups. **Conclusion:** Our results provide evidence for commonalities in brain dysfunction between ADHD and BD. Theta power may play a role as a marker of neurobiological processes in both disorders.

## 2.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) are common psychiatric disorders, respectively affecting around 2-4% and 1-2% of the adult population worldwide (Merikangas et al., 2011; Willcutt, 2012). While ADHD and BD denote distinct psychiatric conditions, diagnostic delineation is impeded by considerable symptomatic overlap. Both ADHD and the manic phase of BD are associated with distractibility, restlessness, talkativeness, lack of social inhibition and impulsivity (Galanter & Leibenluft, 2008; Kent & Craddock, 2003). Both disorders further present with features of mood dysregulation, such as irritability and emotional lability (Kitsune et al., under review; Skirrow et al., 2014, 2012). However, ADHD symptoms are chronic and trait-like, while BD symptoms tend to occur for distinct periods of time (Asherson et al., 2014). Nevertheless, symptoms of distractibility and mood dysregulation (Najt et al., 2007; Newman & Meyer, 2014; Peluso et al., 2007), as well as residual cognitive and functional impairments (Henry et al., 2013; Torres, Boudreau, & Yatham, 2007), persist as milder stable traits in euthymic BD. Such overlap can lead to challenges in distinguishing the two disorders in clinical practice and may, consequently, result in inappropriate treatment decisions (Asherson et al., 2014).

Similar cognitive impairments have been described for individuals with ADHD and BD. Both ADHD and euthymic BD are associated with poor accuracy in attentional and inhibitory processing tasks (Arts et al., 2008; McLoughlin et al., 2010; Robinson & Ferrier, 2006; Torralva et al., 2011), as well as with increased reaction time variability (RTV) (Adleman et al., 2014; Brotman et al., 2009; Kuntsi & Klein, 2012; Kuntsi et al., 2010). Yet, similar cognitive performance could stem from differing underlying mechanisms (Banaschewski & Brandeis, 2007). Consequently, our recent cognitive-neurophysiological investigations of attentional and inhibitory processing in women with ADHD and women with BD revealed evidence for disorder-specific impairments, despite indistinguishable cognitive performance (Michellini et al., 2015). Event-related potential (ERP) analysis showed significantly reduced N2 amplitude in participants with BD, compared to the ADHD and control groups, in response to NoGo stimuli during a cued continuous performance task (CPT-OX) (Michellini et al., 2015). As the

N2 in response to NoGo stimuli, or in incongruent trials, is considered to reflect conflict-monitoring processing (Yeung & Cohen, 2006), the results suggest impaired conflict monitoring in women with BD, compared to women with ADHD and control women. Yet, women with ADHD and women with BD also showed overlapping neurophysiological impairments compared to controls on the NoGo-P3, suggesting shared inhibitory control deficits (Michelini et al., 2015).

Another method to investigate covert processing and other underlying mechanisms in the absence of overt performance differences is employing quantitative electroencephalography (QEEG). QEEG allows the direct examination of subtle changes in cortical activity, which may reflect state regulation and arousal (Banaschewski & Brandeis, 2007). This is of particular relevance in conditions such as ADHD and BD, which show abnormalities in state regulation and arousal (Cortese et al., 2012; Degabriele & Lagopoulos, 2009; Nigg, 2013; Ongür et al., 2010). In QEEG, electrophysiological recordings are quantified in the frequency ranges delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz) and gamma (>30 Hz). The most frequently reported findings of QEEG studies in children and adults with ADHD during resting-state conditions are elevated power in slow frequency bands (delta and theta), reduced power in fast wave cortical activity (mainly beta) and an elevated proportion of slower to faster frequencies in the brain, as reflected by the theta:beta ratio (TBR) (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke et al., 2003a, 2006, 2008; Cooper et al., 2014; Koehler et al., 2009; Snyder & Hall, 2006). Yet, several recent studies have failed to replicate these findings (Buyck & Wiersema, 2014; Kitsune et al., 2015; Liechti et al., 2013; Loo et al., 2009; Ogrim et al., 2012; Poil et al., 2014; Skirrow et al., 2015) and the increased TBR as a marker of ADHD diagnosis is being contested (Arns et al., 2013; Jeste et al., 2015; Lenartowicz & Loo, 2014). EEG spectral power in ADHD further seems to depend on the context: one study found elevated delta and theta activity in individuals with ADHD compared to controls during the resting-state condition at the start of recording sessions, and increased beta power in the ADHD group compared to controls at the end of the recording session (Kitsune et al., 2015). In BD, elevated delta and theta power, as well as decreased alpha power, have been reported during resting-state conditions (Başar et al., 2012; Clementz, Sponheim, Iacono, & Beiser, 1994; Degabriele &

Lagopoulos, 2009). However, direct QEEG comparison studies between ADHD and BD have not yet been conducted.

Few studies on ADHD have examined cortical activity patterns during cognitive task conditions and findings are inconsistent. While some studies have shown no differences in cortical activation between controls and individuals with ADHD during a CPT (Loo et al., 2009; Skirrow et al., 2015), others have reported elevated alpha (Nazari et al., 2011; Swartwood et al., 2003) and theta power (El-Sayed et al., 2002) in individuals with ADHD compared to controls. In addition, lower theta power in adults with ADHD has been demonstrated in the Sustained Attention to Response Task (SART), owing to task-related increases in frontal theta activity in control participants that were absent in participants with ADHD (Skirrow et al., 2015). Treatment with methylphenidate resulted in normalisation of the resting-state to task activation pattern. These findings may indicate a lack of modulation of cortical activity from resting-state to cognitive task in the ADHD group compared to controls. QEEG profiles of individuals with BD during cognitive tasks have not yet been studied. Investigating the oscillatory patterns of individuals with ADHD and BD across condition, from rest to cognitive task condition, may allow us to investigate cortical activation and arousal patterns that could inform us on impairments that are specific to or shared between the disorders.

The aim of the present study was to test whether QEEG identifies differences or similarities between women with ADHD, women with BD and controls during a resting-state condition (eyes open, EO) and an active task condition (a CPT with flankers), which could inform us on the potentially overlapping and distinct electrophysiological impairments in both disorders that may underlie symptomatic and cognitive similarities. In addition, we aim to investigate how EEG patterns change in relation to recording condition (rest vs. cognitive task condition).



## **2.3 Method**

### **2.3.1 Sample**

The sample consisted of 20 women with ADHD, 20 women with euthymic BD and 20 control women. Participants with ADHD were recruited from the Adult ADHD Clinic at the Maudsley Hospital, London, UK. Participants with BD were recruited from the Maudsley Psychosis Clinic, London, UK, or had previously participated in another research study (Hosang, Uher, Maughan, McGuffin, & Farmer, 2012). Control participants were recruited from the Mindsearch volunteer database maintained by the Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK, which comprises several thousand potential participants. Participants for this study were randomly selected from all those meeting inclusion criteria.

In the clinical groups, diagnosis was confirmed from medical records, following Diagnostic and Statistical Manual (DSM-IV) criteria (American Psychiatric Association, 2000). The ADHD participants met current criteria for combined-type ADHD or inattentive-type ADHD with sufficient symptoms of hyperactivity-impulsivity in the past to meet a childhood combined-type diagnosis. Participants in the BD group had a diagnosis of bipolar I disorder (BD-I), with evidence of a past manic episode lasting one week or more. BD-I patients were selected if they were currently euthymic. Exclusion criteria for all groups were drug or alcohol dependency in the last six months, autism, epilepsy, neurological disorders, brain injury, past electroconvulsive therapy (ECT), current involvement in another research trial likely to alter symptom severity, pregnancy or limited proficiency in the English language. Those with a reported comorbidity of ADHD and BD, or who were currently experiencing a manic episode, were also excluded. In addition, control participants, who reported a history of psychiatric disorders, or who were taking psychiatric medication, were excluded from the study.

Participants' IQs were assessed with the Wechsler Abbreviated Scale of Intelligence - Fourth Edition (WASI-IV; Wechsler 1999). IQ ( $F_{2,59}=1.37$ ,  $p=0.26$ ) and age ( $F_{2,59}=1.63$ ,  $p=0.21$ ), which ranged from 20 to 52 years, did not differ between groups (Table 2.1). Participants with ADHD were asked to come off

stimulant medication 48 h before the assessment. For ethical reasons, participants were not asked to stop taking mood stabilisers (70% of the BD group), anti-psychotic medication (40% of the BD group) or anti-depressants (7% of the ADHD group and 25% of the BD group), which they had been prescribed. Ethical approval for the study was granted by the Camberwell St Giles Research Ethics Committee (11/LO/0438) and all participants provided informed consent.

**Table 2.1. Descriptive statistics.**

	<b>ADHD</b> (n=20)	<b>BD</b> (n=20)	<b>Controls</b> (n=20)	<b>p-value</b>
<b>Age in years (SD)</b>	37.4 (7.6)	40.3 (7.7)	36.7 (4.3)	0.21
<b>IQ (SD)</b>	104.5 (17.9)	108.0 (12.5)	112.4 (14.2)	0.26

### ***2.3.2 Procedure and cognitive-performance measures***

Participants attended a single 4.5 h research session, which included an EEG assessment, an IQ test and clinical interviews. As part of the EEG assessment, participants completed a 3-minute eyes-open resting-state condition (EO), as well as a 3-minute eyes-closed resting-state condition, prior to performing on a CPT with flankers (CPT-OX) (Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011). In line with recent research (Nazari et al., 2011; Skirrow et al., 2015), QEEG differences between EO and CPT-OX are analysed here.

The CPT-OX is a cued Go/NoGo task that probes attention, preparation and response inhibition. The task consisted of 400 black letter arrays, made up of a centre letter and incompatible flankers on each side to increase. The presented arrays included the cue letter 'O', the target letter 'X' as well as the distractors 'H', 'B', 'C', 'D', 'E', 'F', 'G', 'J' and 'L'. Letters were presented centrally on the computer monitor, subtending approximately 5°. Cue and target letters ('O' and 'X' respectively) were flanked by incompatible letters ('XOX' and 'OXO' respectively). Participants were instructed to ignore the flanking letters and

respond as quickly as possible to cue-target sequences ('O'-'X'). 80 cues ('XOX') were followed by the target ('OXO') in 40 trials (Go condition), and by neutral distractors in the remainder of trials (NoGo condition). On 40 trials, the target letter 'X' was not preceded by a cue 'O' and had to be ignored. Letters were presented every 1.65 s for 150 ms in a pseudo-randomised order. Ten practice trials preceded the main task and were repeated, if required, to ensure participant comprehension. Participants were instructed to respond only to Cue-Go sequences by pressing a button as quickly as possible with the index finger of their preferred hand. Participants were further asked to withhold the response in the presence of a NoGo stimulus, in the presence of a Go stimulus not preceded by a cue, or in the presence of any other irrelevant letters. Task duration was 11 min.

### ***2.3.3 Electrophysiological recording and analysis***

The EEG was recorded from a 62 channel direct-current-coupled recording system (extended 10–20 montage), using a 500 Hz sampling-rate, impedances under 10 k $\Omega$  and FCz as the recording reference. The electro-oculograms were recorded from electrodes above and below the left eye and at the outer canthi. Participants were seated on a height-adjustable chair in a dimly-lit video-monitored testing cubicle. Stimuli were presented on a computer monitor at a distance of approximately 120 cm, using the Presentation software package ([www.neurobs.com](http://www.neurobs.com)). EEG data were analysed using Brain Vision Analyzer 2.0 (Brain Products, Germany). Researchers were blind to group status during EEG pre-processing and analysis. Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and digitally filtered using Butterworth band-pass filters (0.1-30 Hz, 24 dB/oct). All trials were also visually inspected for electrical artefacts (due to electrical noise in the EEG recording) or obvious movement, and sections of data containing artefacts were removed manually. Ocular artefacts, corresponding to blink-related and vertical and horizontal eye movements, were identified using the infomax independent component analysis (ICA) algorithm (Jung et al., 2000), which allows for removal of activity associated with ocular artefacts by back-projection of all but this activity. Sections of data with remaining artefacts exceeding  $\pm 100 \mu\text{V}$  in

any channel or with a voltage step greater than 50  $\mu\text{V}$  were automatically rejected.

Quantitative EEG was investigated for EO and CPT-OX. Data were segmented into 2-second epochs and power spectra were computed using a Fast Fourier Transform (FFT) with a 10% Hanning window. Analyses focused on delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-30 Hz) frequency band differences between ADHD, BD and control groups. All data were log transformed ( $\lg$ ) to normalise the data. To reduce the number of statistical comparisons, EEG power ( $\mu\text{V}^2$ ) within each frequency band was averaged across frontal (Fz, F1, F2, F3, F4, F5, F6, F7, F8), central (Cz, C1, C2, C3, C4, C5, C6) and parietal (Pz, P3, P4, P7, P8) regions from individual scalp electrodes.

### ***2.3.4 Statistical analysis***

A repeated-measures analysis of variance (ANOVA), applying a Greenhouse-Geisser correction when appropriate, was carried out to investigate diagnostic status-related differences between ADHD, BD and controls in EEG power. Recording condition (EO, CPT-OX) and recording site (frontal, central, parietal) were used as within-subject variables and diagnostic status (ADHD, BD, control) as between-subjects variable. Delta, theta, alpha and beta power were each investigated with a 2 x 3 x 3 repeated-measures ANOVA. Bonferroni correction was implemented to correct for multiple testing in the different frequency bands: Bonferroni-adjusted  $p\text{-value}=0.0125$ . Post-hoc analyses were carried out using independent samples t-tests for between-subjects contrasts, and paired samples t-tests for within-individual task related differences in EEG power. Effect size (Cohen's  $d$ ), which was calculated using the difference in the means divided by the pooled standard deviation, is also reported (Cohen, 1988). According to Cohen (1988),  $d=0.20$  constitutes a small effect,  $d=0.50$  a medium effect and  $d=0.80$  a large effect.

## 2.4 Results

### 2.4.1 EEG power

Repeated-measures ANOVAs indicated no significant mean effects of group for delta ( $F_{1,57}=1.29$ ,  $p=0.28$ ), theta ( $F_{1,57}=1.70$ ,  $p=0.19$ ), alpha ( $F_{1,57}=1.20$ ,  $p=0.31$ ) or beta ( $F_{1,57}=0.44$ ,  $p=0.65$ ) power.

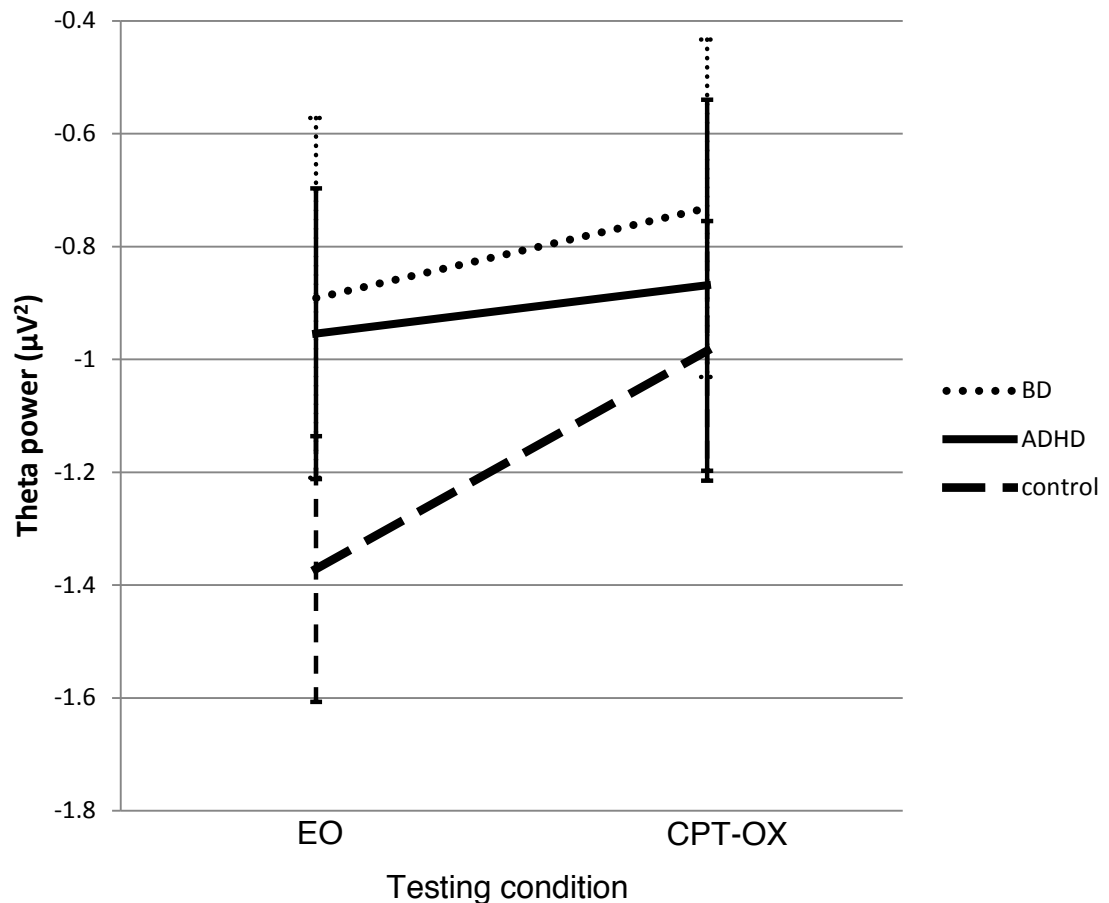
A significant main effect of recording site was identified for theta ( $F_{1,57}=43.90$ ,  $p<0.001$ ), with significantly lower theta power in frontal than central ( $t=-24.28$ ,  $df=59$ ,  $p<0.001$ ) and parietal locations ( $t=-29.32$ ,  $df=59$ ,  $p<0.001$ ). Central theta power was also significantly lower than parietal theta power ( $t=12.50$ ,  $df=59$ ,  $p<0.001$ ). No significant condition-by-site-by-group interaction emerged ( $F_{1,57}=1.39$ ,  $p=0.241$ ).

Significant main effects of testing condition emerged for delta ( $F_{1,57}=85.43$ ,  $p<0.01$ ), alpha ( $F_{1,57}=16.53$ ,  $p<0.01$ ) and beta power ( $F_{1,57}=14.73$ ,  $p<0.01$ ), but not for theta power ( $F_{1,57}=0.29$ ,  $p=0.600$ ).

No significant group-by-condition interaction emerged for delta ( $F_{1,57}=2.20$ ,  $p=0.073$ ), alpha ( $F_{1,57}=1.29$ ,  $p=0.278$ ) or beta power ( $F_{1,57}=2.04$ ,  $p=0.093$ ). Consequently, the results for these frequency bands are not reported further.

A significant group-by-condition interaction emerged for theta power ( $F_{1,57}=6.15$ ,  $p=0.004$ ). Post-hoc tests revealed significantly higher theta power in the ADHD group compared to controls during EO ( $t=2.50$ ,  $df=38$ ,  $p=0.017$ ), with medium-to-large effect size ( $d=0.72$ ), but the ADHD and control groups did not differ in theta power during CPT-OX ( $t=0.61$ ,  $df=38$ ,  $p=0.548$ ). Post-hoc tests further demonstrated significantly higher theta power in the BD group compared to controls during EO ( $t=2.54$ ,  $df=38$ ,  $p=0.016$ ), with medium-to-large effect size ( $d=0.74$ ), but the BD and control groups did not differ in theta power during CPT-OX ( $t=1.40$ ,  $df=38$ ,  $p=0.169$ ). Moreover, no significant differences in theta power emerged between the ADHD and BD groups during EO ( $t=0.32$ ,  $df=38$ ,  $p=0.748$ ) or CPT-OX ( $t=0.64$ ,  $df=38$ ,  $p=0.524$ ). While control participants showed a task-related increase in theta power ( $t=3.34$ ,  $df=19$ ,  $p=0.003$ ), with medium effect size ( $d=0.59$ ), no significant changes in theta power from EO to

CPT-OX were observed in the ADHD ( $t=-1.23$ ,  $df=19$ ,  $p=0.235$ ) or BD groups ( $t=-1.50$ ,  $df=19$ ,  $p=0.150$ ) (Figure 2.1). These group differences in rest-to-task transition effects in theta power likely drive the significant group-by-condition interaction.



**Figure 2.1. Mean theta power across resting-state (EO) and task (CPT-OX) condition in women with adult ADHD, women with bipolar disorder (BD) and control women.** Error bars represent 95% confidence intervals.

## 2.5 Discussion

In this study investigating the relationship of EEG indices of cortical activity in women with ADHD, women with BD and control women, both ADHD and BD participants showed higher theta power than controls during the resting-state condition. No significant differences emerged between the two clinical groups. While control participants showed a task-related increase in theta activity from resting-state to cognitive task, no significant changes in theta power were observed in the ADHD or BD groups. Our results provide evidence for

commonalities in brain dysfunction between ADHD and BD. Theta power may act as a marker of neurobiological processes in both disorders.

Both the ADHD and BD groups showed an elevation of theta power during the resting-state condition, compared to controls. To date, no study has directly compared the cortical activity patterns of individuals with ADHD and BD. This finding suggests commonalities in oscillation patterns between women with ADHD and BD. The lack of significant differences between the clinical groups adds to previous research, which has shown an elevation of theta power during resting-state conditions independently in individuals with ADHD (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke et al., 2003a, 2006, 2008; Koehler et al., 2009; Snyder & Hall, 2006) and in individuals with BD (Degabriele & Lagopoulos, 2009), compared to controls. It is not fully understood what increased theta power in individuals with ADHD and BD during resting-state conditions represents. The findings of elevated resting theta power in younger compared to older neurotypical children (Benninger et al., 1984; Gasser, Jennen-Steinmetz, et al., 1988; Gasser, Verleger, et al., 1988) led to the development of a maturational-lag hypothesis (Kinsbourne, 1973). This hypothesis holds that there is a delay in central nervous system (CNS) development in individuals with ADHD because during neurotypical CNS maturation, slow wave activity is replaced with fast wave activity. Yet, this study and other research demonstrating elevated theta power in adolescents and adults with ADHD (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke et al., 2008; Kitsune et al., 2015; Koehler et al., 2009; Skirrow et al., 2015) and BD (Degabriele & Lagopoulos, 2009) do not support this hypothesis. Increased theta power in individuals with ADHD during resting-state conditions has also been interpreted as representing hypo-arousal (Lubar, 1991; Satterfield & Dawson, 1971). Yet, two studies investigating the relationship between resting EEG power and skin conductance level (another marker of CNS arousal) in children with and without ADHD linked increased alpha rather than theta to under-arousal as indexed by skin conductance levels (Barry et al., 2004, 2009). While the significance of increased theta power during resting-state conditions remains to be fully elucidated, our findings may suggest a role for theta power as a common marker of neurobiological processes in both ADHD and BD. This is in line with findings from quantitative genetics studies, which have found

strong phenotypic and genetic links between ADHD and abnormal theta activity, suggesting it may be a biological marker or intermediate phenotype (endophenotype) for ADHD (McLoughlin, Palmer, et al., 2014; Tye, Rijdsdijk, et al., 2014).

In addition, no differences in EEG power were observed between the three groups during the cognitive task condition and no change in theta from resting-state to task condition in the clinical groups was found. Our study is the first to investigate the QEEG profile of individuals with BD during a cognitive task and to directly compare it to an ADHD group. The findings, therefore, suggest commonalities in brain dysfunction between ADHD and BD during this cognitive task. Furthermore, the current study is the first to investigate the EEG patterns during both rest and task condition in women with adult ADHD. The results support previous work in an all-male sample, which showed no differences in cortical activation between controls and individuals with ADHD during the CPT and no change in spectral power from rest to cognitive task (Skirrow et al., 2015). Yet, previous QEEG studies have yielded inconsistent results, such as elevated alpha (Nazari et al., 2011; Swartwood et al., 2003) and theta power (El-Sayed et al., 2002) on switching from resting-state to CPT in individuals with ADHD compared to controls. The seeming lack of task-dependent modulation of theta power in ADHD and BD participants may be explained by abnormalities in the default mode network (DMN), which is typically activated during resting-state conditions and deactivated during task performance (Broyd et al., 2009; Raichle, 2010). Abnormalities in the DMN during rest have been demonstrated in both ADHD and BD (Cortese et al., 2012; Ongür et al., 2010). Yet, while task-related modulation remains to be examined in BD, the DMN has been found to be inadequately attenuated when individuals with ADHD perform a task (Cortese et al., 2012; Fassbender et al., 2009; Sonuga-Barke & Castellanos, 2007). The absence of task-related changes in theta power in our sample of women with ADHD and BD, as well as in previous research on ADHD (Skirrow et al., 2015), might therefore indicate inadequate attenuation of the DMN. A recent review, summarising findings from studies employing functional magnetic resonance imaging (fMRI) and EEG simultaneously, provides support for this idea (Nishida et al., 2015), by concluding that increased frontal theta power



indexes decreased DMN activity. Consequently, theta power may be vital to the attenuating processes required for cognitive functioning.

Unlike previous research, this study did not find decreased beta activity in individuals with ADHD (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke et al., 2008; Koehler et al., 2009) or elevated delta power in individuals with BD (Degabriele & Lagopoulos, 2009). These discrepancies may be due to age and gender effects. Our all-female sample had a mean age of 38 years and an age range of 20 to 52 years. As EEG power tends to decline with age (Lüchinger, Michels, Martin, & Brandeis, 2011; Michels et al., 2013; Poil et al., 2014), this wide age range may have reduced power to detect differences of smaller effect between the groups. Yet, some recent studies have also failed to replicate previous findings of decreased beta power in ADHD (Buyck & Wiersema, 2014; Liechti et al., 2013; Loo et al., 2009; Ogrim et al., 2012; Poil et al., 2014; Skirrow et al., 2015). A recent meta-analysis demonstrated that the reported effect size for TBR abnormalities in ADHD showed a strong relationship with year of publication, declining over time (Arns et al., 2013). The paper proposes the trend for reduced sleep duration in children across time, as well as sample and testing context differences between studies, as possible explanations. Support for context effects comes from a study of resting-state EEG power differences between recordings made at the beginning and the end of a 1.5 h testing session in 76 adolescents and young adults with ADHD and 85 controls, which showed elevated delta and theta power in the ADHD group in the beginning and elevated beta power in the ADHD group at the end of the testing session (Kitsune et al., 2015).

Several limitations should be considered alongside these results. First, medication status differed between the groups. While participants with ADHD were asked to come off their stimulant medication 48 hours before the assessment, participants were not asked to stop taking their mood-stabilising, anti-psychotic or anti-depressant medication for ethical reasons. We were further not able to directly test the effect of medication on EEG power, given the small number of individuals in the various medication sub-groups. Although the understanding of the effects of medications on QEEG is still limited, no significant differences between medicated and unmedicated individuals with

euthymic BD on QEEG have been found (Degabriele & Lagopoulos, 2009; El-Badri, Ashton, Moore, Marsh, & Ferrier, 2001). It is, therefore, unlikely that medication effects produced the results in this study. However, medication cannot be excluded as potential confounder and studies of non-medicated individuals are needed to elucidate the effects of medication on EEG power. Second, we examined cortical activation for the frequency bands alpha, beta, delta and theta. While some researchers have advocated abandoning fixed frequency bands (Klimesch, 1999), the grouping of these frequencies into the particular bands has occurred historically and makes comparison between studies easier. For finer resolution and increased signal to noise ratio, future studies may conduct source based analyses such as independent component analysis (ICA). Finally, this investigation was conducted in a homogenous all-female sample. Future studies will need to replicate these findings in larger samples of both genders, in order to generalise these findings to more typical clinical populations.

Our results provide evidence for commonalities in brain dysfunction between ADHD and BD, with theta power potentially playing a role as a marker of shared neurobiological processes in both disorders. In light of shared cognitive impairments and the overlapping symptomatology of ADHD and BD, these findings represent a move towards uncovering biological markers underlying the pathophysiology shared between the disorders. Currently, diagnostic manuals such as the DSM (American Psychiatric Association, 2000, 2013) outline clinical diagnoses in a categorical system based on the description of behavioural symptoms. Yet, research has revealed substantial evidence for pathophysiological heterogeneity within disorders (Burdick, Ketter, Goldberg, & Calabrese, 2015; Jeste et al., 2015; Sjöwall, Roth, Lindqvist, & Thorell, 2013), as well as pathogenic overlap between disorders (Lee et al., 2013; Michelini et al., 2015). Consequently, diagnostic boundaries based on behavioural symptoms do not seem to correspond seamlessly to findings from neuropsychological and genetic studies, and have been only moderately successful at predicting treatment outcome (Insel et al., 2010; Ostacher et al., 2015; Retz & Retz-Junginger, 2014). Future studies should build on the results from this and similar studies to understand the relationship between behaviour, neurophysiology and the genome to identify syndromes based on

pathophysiology. This could lead to more objective and precise approaches to diagnosis and prognosis and may eventually result in improved interventions and long-term outcome (Casey, Oliveri, & Insel, 2014).

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## Chapter 3. Altered EEG spectral power in adolescents with ADHD and preterm born adolescents during rest and cognitive performance

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### 3.1 Abstract

**Background:** Preterm birth has been associated with an increased risk for ADHD-like symptoms and cognitive impairments similar to those seen in ADHD. However, direct comparisons across ADHD and preterm birth on neurophysiological measures are limited. The aim of this analysis was to test whether quantitative EEG (QEEG) measures identify differences or similarities between term-born adolescents with ADHD and adolescents born preterm during resting-state and cognitive task conditions. In addition, we aimed to investigate age effects on EEG spectral power. **Methods:** First, we directly compared QEEG activity between 75 term-born adolescents with ADHD, 145 adolescents born preterm and 153 term-born control adolescents during an eyes-open resting-state condition (EO) and a cued continuous performance task (CPT-OX). Although age was statistically controlled in the analysis, we reran all analyses on a carefully age-matched subsample, due to significant group mean differences in age and the possibility of strong age effects on QEEG activity. This sub-sample comprised 36 term-born adolescents with ADHD, 94 preterm-born adolescents and 63 control adolescents. We also examined the relationship between age and EEG spectral power in the full sample using correlation analyses. **Results:** Age had a strong effect on delta power in the full sample, as demonstrated by correlations of  $r=-0.50$ – $-0.64$ , as well as by differences in results between the full sample and the age-matched subsample. We, therefore, interpret the group comparisons from the carefully age-matched analyses only. Delta power was the only frequency range to demonstrate a significant group-by-condition interaction. The ADHD group did not differ significantly from the preterm and control groups during EO with regard to delta power, but during CPT-OX the ADHD group showed significantly increased delta power compared to both the preterm and control groups. The preterm group did not differ significantly from the control group on delta power during EO or CPT-OX. Rest-to-task transition effects in the delta band differed between the groups: while the ADHD and control groups demonstrated a

significant increase in delta power from EO to CPT-OX, no change in delta power from EO to CPT-OX was found in the preterm group. **Conclusion:** Our results provide evidence for differences in delta power between term-born adolescents with ADHD and adolescents born preterm, as well as for maturational effects on EEG spectral power. Future large-scale studies are needed to elucidate how the cortical activation patterns and rest-to-task transition effects observed in adolescents born preterm mediate cognitive impairments and clinical symptoms.

## 3.2 Introduction

Preterm births, denoting births before 37 completed weeks of gestation (World Health Organization, 1977), are highly prevalent. In the developed world, 8.6% of individuals are born preterm (Blencowe et al., 2012). Although the survival rates for individuals born preterm have increased greatly over the last decades (Goldenberg et al. 2008), preterm birth is a type of pre- and peri-natal trauma that increases the risk of adverse long-term outcomes (Bhutta et al., 2002; D’Onofrio et al., 2013), possibly because the late third trimester (32–40 weeks’ gestation) serves as a critical period to lay the foundation of brain networks (Ball et al., 2014; van den Heuvel et al., 2014). A cognitive profile that resembles those of individuals with ADHD, including deficits in attention and inhibitory control (Aarnoudse-Moens et al., 2009; Geva & Feldman, 2008; Lawrence et al., 2009; Miskovic et al., 2009; Mulder et al., 2009; Nosarti et al., 2006), as well as ADHD diagnosis, are frequently associated with preterm birth (Bhutta et al., 2002; D’Onofrio et al., 2013; Halmøy et al., 2012; Lindström et al., 2007). Yet, it is unclear whether the symptoms and deficits seen in individuals born preterm are identical to those associated with ADHD or whether they are part of more wide-ranging impairments.

Quantitative electroencephalography (QEEG), which measures the strength of electrical activity along the scalp, allows investigation of covert processes due to its sensitivity to subtle changes in the power of oscillatory activity and its high temporal resolution (Banaschewski & Brandeis, 2007). QEEG is, therefore, a useful tool to examine and compare the neurocognitive profiles of individuals with ADHD and preterm-born individuals. Electrophysiological recordings are quantified and conventionally described in the following frequency bands: delta (0.5-3.5 Hz), theta (3.5-7.5Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz) and gamma (>30 Hz). Traditionally, elevated power in slow (delta and theta) and reduced power in fast (mainly beta) frequency bands have been reported for children (Bresnahan et al., 1999; Clarke et al., 2003a, 2006; Snyder & Hall, 2006) and adults (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke et al., 2008; Koehler et al., 2009) with ADHD during resting-state conditions. However, a number of recent studies have not replicated these findings (Buyck

& Wiersema, 2014; Kitsune et al., 2015; Liechti et al., 2013; Loo et al., 2009; Ogrim et al., 2012; Poil et al., 2014; Skirrow et al., 2015).

Although several EEG studies have examined the neurophysiology of preterm-born infants in neonatal intensive care units (Meijer et al., 2014; Victor et al., 2005) and in the postnatal period (Beckwith & Parmelee, 1986; Duffy et al., 1990; González et al., 2011; Hayakawa et al., 2001; Vecchierini et al., 2007), few EEG studies have been conducted in children, adolescents and adults born preterm. One study that investigated spectral EEG power in children with educational problems during an eyes-closed resting condition reported increased theta (3.6-5 Hz), beta (20.1-30 Hz) and gamma (30.1-40.2 Hz) power in preterm born children (n=38) compared to term-born controls with education problems (n=22) (Rozhkova, 2008). A second study investigated QEEG in young adults who were born preterm and at extremely low birth weight (n=71; mean birth weight=874 g, mean gestational age=27.5 weeks), and who were not impaired in adulthood (defined as being free of neurosensory impairments and psychiatric disorders). This study found increased power in the slow (delta and theta) and decreased power in the fast (alpha and beta) frequency bands in preterm-born individuals compared to term-born controls with healthy birth weight (n=83) during a resting-state condition (Miskovic et al., 2009). While it is now possible to study survivors of preterm birth due to major advances in neonatal care over the last few decades (Goldenberg et al. 2008), the cortical activation patterns of adolescents born preterm remain to be assessed. In addition, no study to date has directly compared cortical activation between individuals born preterm and individuals with ADHD.

Relative power in slow (delta and theta) and fast (alpha and beta) frequency bands have been indicated as reliable markers of typical development, respectively decreasing and increasing across the lifespan (Clarke, Barry, McCarthy, & Selikowitz, 2001; Gasser, Verleger, et al., 1988; John et al., 1980; Matoušek & Petersén, 1973; Somsen, van't Klooster, van der Molen, van Leeuwen, & Licht, 1997). Consequently, the findings of elevated power in slow and reduced power in fast frequency bands reported in ADHD have been interpreted as maturational delay (Clarke et al., 2001; Kinsbourne, 1973). QEEG studies of ADHD have shown maturational effects similar to those in

typically developing individuals (i.e. increased power in slow and decreased power in fast frequency bands in children compared to adolescents and adults) (Buyck & Wiersema, 2014; Liechti et al., 2013; Monastra, Lubar, & Linden, 2001). Yet, research on the development of EEG spectral power in individuals with ADHD compared to age-matched controls has yielded inconsistent results. One study found elevated theta power in ADHD throughout the lifespan (Bresnahan et al., 1999), whereas other studies showed atypical developmental trajectories in individuals with ADHD during late childhood (Liechti et al., 2013) or adulthood (Poil et al., 2014). While cognitive impairments in individuals born preterm persist into adolescence (Burnett et al., 2015; Taylor et al., 2004) and adulthood (Nosarti et al., 2007; Stålnacke et al., 2014), little is known about EEG maturation effects in individuals born preterm. In the first weeks and months after birth, marked developmental changes in background EEG activity occur in preterm born infants (Biagioni et al., 1994; Hayakawa et al., 2001; Myers et al., 2012; Nunes, Khan, Gomes Filho, Booij, & da Costa, 2014; Okumura et al., 2003; Vecchierini et al., 2007). However, no conclusion on EEG maturation across the lifespan can be drawn from these findings.

Research examining oscillatory patterns during cognitive task performance in ADHD has yielded inconsistent results. While some studies have reported no differences in EEG power between controls and individuals with ADHD during a continuous performance test (CPT) (Loo et al., 2009; Skirrow et al., 2015, chapter 2), others have reported elevated alpha (Nazari et al., 2011; Swartwood et al., 2003) and theta power (El-Sayed et al., 2002) in individuals with ADHD compared to controls. The lack of significant differences in EEG spectral power between controls and individuals with ADHD during the CPT was likely driven by the absence of rest-to-task transition effects in the ADHD group (i.e. no changes in spectral power from resting-state to cognitive task) in two of the studies reviewed above (Skirrow et al., 2015, chapter 2). To date, no studies have examined the QEEG profile of preterm born individuals during cognitive task performance.

The aim of the present study is to test whether QEEG measures identify differences or similarities between adolescents with ADHD, adolescents born preterm and control adolescents during a resting-state condition (eyes open,



EO) and a cognitive task condition (a CPT with flankers, CPT-OX (van Leeuwen et al., 1998)) to elucidate whether potential impairments observed among individuals born preterm are identical to those seen in term-born individuals with ADHD. As part of this investigation, we examine how EEG patterns change in relation to recording condition (resting vs. cognitive task) to examine task-related modulation of EEG spectral power in adolescents with ADHD and adolescents born preterm. Although the full sample consists entirely of adolescents, significant differences in age emerge between the groups (Table 3.1). To address this issue, age is controlled for statistically in the analysis of the full sample. In addition, all analyses are rerun using a carefully age-matched subsample. We further aim to explore the effect of age on QEEG within these three groups of the full sample using correlation analyses. If diverging results in the age-matched subsample and significant correlations between age and EEG spectral power emerge, the findings from the age-matched subsample, rather than from the full sample, are discussed and interpreted because of apparent age effects.

### **3.3 Method**

#### ***3.3.1 Sample***

ADHD and control sibling pairs who had taken part in previous research (Chen et al., 2008; Kuntsi et al., 2010; Wood, Asherson, Rijdsdijk, & Kuntsi, 2009), were invited to take part in a follow-up study (Cheung et al., 2015a, 2015b). All participants were of European Caucasian decent and had one or more full siblings available for ascertainment. Initially, participants with ADHD were included if they had a clinical diagnosis of DSM-IV combined-type ADHD during childhood. At follow-up, participants in the ADHD group were included if, as well as having an ADHD diagnosis in childhood, they met DSM-IV criteria for any ADHD subtype at follow-up. The control group was initially recruited from primary (ages 6–11 years) and secondary (ages 12–18 years) schools in the UK, aiming for an age- and sex-match with the ADHD sample. Control individuals were included in the study if they did not meet DSM-IV criteria for any ADHD subtype either in childhood or at follow-up. Exclusion criteria for both groups included IQ<70, autism, epilepsy, general learning difficulties, brain

disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD.

We followed up the sample on average 5.8 years ( $SD=1.1$ ) after initial assessments. Siblings of individuals with ADHD were included in the ADHD group if they met DSM-IV criteria for any ADHD subtype at follow-up. Siblings of control individuals were included in the control group if they did not meet DSM-IV criteria for any ADHD subtype at follow-up. The ADHD and control groups were previously included in a study investigating ADHD case-control differences on cognitive and neurophysiological markers of ADHD persistence and remission (Cheung et al., 2015a). While ADHD-control differences for this sample have been reported previously, here, a subsample of the ADHD and control groups is compared to a group of preterm-born adolescents.

At follow-up, six participants from the ADHD-sibling pair sample were excluded from the group analyses, as they had missing parent ratings of clinical impairment and their current ADHD status could not be determined. Two additional participants from the ADHD-sibling pair sample were excluded because they became very drowsy during the cognitive task and fell asleep. In two cases there was EEG equipment failure, resulting in exclusion. Seven participants from the ADHD-sibling pair sample, who were born preterm, as well as 38 individuals from the ADHD-sibling pair sample, who provided no information about gestational age (GA), were also excluded. Two participants with childhood ADHD who did not meet ADHD symptom criteria but met clinical levels of impairment at follow-up were further excluded to minimize heterogeneity in the ADHD sample.

Since age has a large effect on QEEG measures (Clarke et al., 2001; Gasser, Verleger, et al., 1988; John et al., 1980; Matoušek & Petersén, 1973; Somsen et al., 1997), we chose to also analyse a homogeneous group of participants with regard to age. For this subsample, we excluded an additional 37 individuals from the ADHD-sibling pair sample who fell outside the investigated age range (14-19 years). On average, the ADHD group was older than the preterm group.

Forty-five participants from the control-sibling pair sample were excluded because no GA information was available. Six control participants were removed from the analyses for meeting DSM-IV ADHD criteria based on the parent-rated Barkley Informant Rating Scale (Barkley & Murphy, 2006). For the subsample analysis, an additional 66 participants from the control-sibling pair sample were excluded because they fell outside the investigated age range (14-19 years). On average, the control group was older than the preterm group.

The preterm group was recruited from secondary schools in Southeast England. All preterm participants had one or more full siblings available for ascertainment, and were born before 37 weeks' gestation. Siblings of individuals born preterm were included in the preterm group if they were born before 37 weeks' gestation. Exclusion criteria for the preterm group included  $IQ < 70$ , general learning difficulties, cerebral palsy and any other medical conditions that affects motor co-ordination including epilepsy. Three individuals born preterm were excluded because they showed insufficient understanding/engagement with the CPT-OX, as suggested by the testing notes and further indicated by extreme omission errors=17, 31 and 41 respectively, which were more than 3.5 SD from the mean (Tye et al., 2011; Tye, Asherson, et al., 2014). Seven individuals from the preterm-sibling pair sample were excluded because their GA was equal to or above 37 weeks; one individual was excluded because of an  $IQ < 70$  and 26 participants had to be excluded due to EEG equipment failure. For the subsample analysis, an additional 71 individuals from the preterm-sibling pair sample were excluded because they fell outside the investigated age range (14-19 years). On average, the preterm group was younger than the ADHD and control groups. Seven preterm-born individuals in the full sample and three preterm-born individuals in the age-matched subsample met diagnostic criteria for a research diagnosis of ADHD. Since, in this thesis, preterm birth is investigated as a potential risk factor for ADHD, individuals who were born preterm and also demonstrate high levels of ADHD symptoms are not excluded from this analysis.

The final full sample consisted of 75 ADHD participants (six sibling pairs and 63 singletons), 145 preterm-born participants (25 sibling pairs and 95 singletons) and 153 controls (69 sibling pairs and 15 singletons). The groups differed

significantly in terms of age, IQ, gender distribution, GA and ADHD symptom scores (Table 3.1). The ADHD group showed significantly higher ADHD symptom scores than both the preterm ( $t=19.57$ ,  $df=175$ ,  $p<0.001$ ) and control groups ( $t=-46.19$ ,  $df=139$ ,  $p<0.001$ ). The preterm group further demonstrated significantly higher ADHD symptom scores than the control group ( $t=-8.85$ ,  $df=178$ ,  $p<0.001$ ). Age was included as a covariate in all analyses. All analyses were rerun with IQ as an additional covariate. Gender was not included as a covariate in the group analyses to avoid controlling for ADHD status (Cheung et al., 2015a). Written informed consent was obtained and the studies were approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58) and the National Research Ethics Service Committee London – Bromley (13/LO/0068).

**Table 3.1. Descriptive statistics.**

	<b>ADHD</b>	<b>Preterm</b>	<b>Control</b>	<b>Statistic</b>	<b>p-value</b>
<b><i>Full sample</i></b>	n=75	n=145	n=153	-	-
<b>GA in weeks (SD)</b>	39.9 (1.4)	33.2 (2.8)	40.0 (1.2)	$z=-19.9$	$<0.001$
<b>IQ (SD)</b>	97.1(13.7)	104.2 (12.5)	110.3 (12.5)	$z=-2.4$	0.015
<b>Age (SD)</b>	18.5 (2.9)	15.3 (1.9)	17.8 (2.1)	$z=-8.1$	$<0.001$
<b>Age range</b>	12.7-25.9	11.0-20.0	11.9-21.6	-	-
<b>Males %</b>	86.7	51.0	75.6	$\chi^2=34.4$	$<0.001$
<b>ADHD symptom score</b>	14.0 (3.0)	3.6 (4.0)	0.0 (0.0)	$t= 6.3$	$<0.001$
<b><i>Age-matched subsample</i></b>	n=36	n=94	n=63	-	-
<b>GA in weeks (SD)</b>	39.72 (1.3)	33.5 (2.4)	40.0 (1.10)	$z=-18.0$	$<0.001$
<b>IQ (SD)</b>	96.4 (14.0)	103.6 (13.2)	108.0 (12.4)	$z=-1.6$	0.112
<b>Age (SD)</b>	16.6 (1.5)	16.4 (1.1)	16.7 (1.0)	$z=-1.7$	0.082
<b>Age range</b>	14.1-18.9	14.8-18.8	14.4-18.1	-	-
<b>Males %</b>	88.9	44.7	47.5	$\chi^2=24.1$	$<0.001$
<b>ADHD symptom score</b>	14.2 (3.0)	3.5 (3.8)	0.0 (0.0)	$t= 3.4$	$<0.001$

The final age-matched subsample consisted of 36 ADHD participants (five sibling pairs and 26 singletons), 94 preterm-born participants (13 sibling pairs and 68 singletons) and 63 controls (eight sibling pairs and 47 singletons). The groups did not differ in terms of age or IQ (Table 3.1). Significant differences in gender distribution, GA and ADHD symptom scores were observed. The ADHD group showed significantly higher ADHD symptom scores than both the preterm ( $t=14.62$ ,  $df=113$ ,  $p<0.001$ ) and the control groups ( $t=-35.25$ ,  $df=84$ ,  $p<0.001$ ). The preterm group further demonstrated significantly higher ADHD symptom scores than the control group ( $t=-6.72$ ,  $df=133$ ,  $p<0.001$ ). Gender was not included as a covariate in the group analyses to avoid controlling for ADHD status (Cheung et al., 2015a).

### **3.3.2 Procedure**

Participants attended a single 4.5 h research session, which included an EEG assessment, an IQ test and clinical interviews. As part of the EEG assessment, participants completed a 3-minute eyes-open resting-state condition (EO), as well as a 3-minute eyes-closed resting-state condition, prior to performing on a CPT with flankers (CPT-OX) (Doehnert et al., 2010; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011). Participants were requested to remain as still as possible, and keep their eyes on a fixed point in front of them for the duration of the recording. A 48 h ADHD medication-free period was required before the research session.

### **3.3.3 Measures**

#### **3.3.3.1 ADHD diagnosis**

In the ADHD group, ADHD was assessed using parental ADHD symptom ratings on the Diagnostic Interview for ADHD in adults (DIVA) (Kooij & Francken, 2007) and the Barkley's functional impairment scale (BFIS) (Barkley & Murphy, 2006). The DIVA is a semi-structured interview designed to evaluate the DSM-IV criteria for both adult and childhood ADHD symptoms and impairment. It consists of 18 items used to define the DSM-IV symptom criteria for ADHD. Each item is scored affirmatively if the behavioural symptom was present *often* within the past six months. Based on DSM-IV criteria, a research

diagnosis of ADHD was made if participants scored six or more on either the inattention or hyperactivity-impulsivity subscales of the DIVA and if they received two or more positive scores on two or more areas of impairment on the BFIS. In the preterm group, ADHD was assessed using parental ADHD symptom ratings on the DIVA (Kooij & Francken, 2007). A research diagnosis of ADHD was made if participants scored six or more on the inattention or hyperactivity-impulsivity subscales of the DIVA.

### *3.3.3.2 IQ*

The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV) (Wechsler, 1999) were administered to all participants to derive an estimate of IQ.

### *3.3.3.3 Cued continuous performance task with flankers*

The CPT-OX is a cued Go/NoGo task that probes attention, preparation and response inhibition. The task consisted of 400 black letter arrays, made up of a centre letter and incompatible flankers on each side to increase difficulty. The presented arrays included the cue letter 'O', the target letter 'X' as well as the distractors 'H', 'B', 'C', 'D', 'E', 'F', 'G', 'J' and 'L'. Letters were presented centrally on the computer monitor, subtending approximately 5°. Cue and target letters ('O' and 'X' respectively) were flanked by incompatible letters ('XOX' and 'OXO' respectively). Participants were instructed to ignore the flanking letters and respond as quickly as possible to cue-target sequences ('O'-'X'). 80 cues ('XOX') were followed by the target ('OXO') in 40 trials (Go condition), and by neutral distractors in the remainder of trials (NoGo condition). On 40 trials, the target letter 'X' was not preceded by a cue 'O' and had to be ignored. Letters were presented every 1.65 s for 150 ms in a pseudo-randomised order. Ten practice trials preceded the main task and were repeated, if required, to ensure participant comprehension. Participants were instructed to respond only to Cue-Go sequences by pressing a button as quickly as possible with the index finger of their preferred hand. Participants were further asked to withhold the response in the presence of a NoGo stimulus, in the presence of a Go stimulus not preceded by a cue, or in the presence of any other irrelevant letters. Task duration was 11 min.

#### *3.3.3.4 EEG recording and analysis*

The EEG was recorded from a 62 channel direct-current-coupled recording system (extended 10–20 montage), using a 500Hz sampling-rate, impedances under 10k $\Omega$  and FCz as the recording reference. The electro-oculograms were recorded from additional electrodes above and below the left eye and at the outer canthi. Participants were seated on a height-adjustable chair in a dimly-lit video-monitored testing cubicle. Stimuli were presented on a computer monitor at a distance of approximately 120 cm, using the Presentation software package ([www.neurobs.com](http://www.neurobs.com)). The EEG data were analysed using Brain Vision Analyzer 2.0 (Brain Products, Germany).

Researchers were blind to group status during EEG pre-processing and analysis. Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and digitally filtered using Butterworth band-pass filters (0.1-30 Hz, 24 dB/oct). All trials were also visually inspected for electrical artefacts (due to electrical noise in the EEG recording) or obvious movement, and sections of data containing artefacts were removed manually. Ocular artefacts, corresponding to blink-related and vertical and horizontal eye movements, were identified using the infomax independent component analysis (ICA) algorithm (Jung et al. 2000), which allows for removal of activity associated with ocular artefacts by back-projection of all but this activity. Sections of data with remaining artefacts exceeding  $\pm 100 \mu\text{V}$  in any channel or with a voltage step greater than 50  $\mu\text{V}$  were automatically rejected.

Prior to performing a CPT-OX (Doehnert et al., 2010; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011), participants carried out a 3-minute eyes-open resting-state condition (EO), as well as a 3-minutes eyes-closed resting-state condition. Here, we focus on the EO and CPT-OX condition in order to be able to compare the findings to recent studies (Nazari et al., 2011; Skirrow et al., 2015) and to findings from chapter 2. Quantitative EEG was investigated for these two conditions (EO and CPT-OX). Data were segmented into 2-second epochs and power spectra were computed using a Fast Fourier Transform (FFT) with a 10% Hanning window. Analyses focus on delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-30 Hz) frequency band differences between ADHD, preterm and control groups. To normalise the data,

all data were log 10 transformed. To reduce the number of statistical comparisons, EEG power ( $\mu V^2$ ) within each frequency band was averaged across frontal (Fz, F1, F2, F3, F4, F5, F6, F7, F8), central (Cz, C1, C2, C3, C4, C5, C6) and parietal (Pz, P3, P4, P7, P8) regions from individual scalp electrodes.

### ***3.3.4 Statistical analysis***

Data were analysed using random intercept models in Stata, to control for non-independence of the data, i.e. data coming from siblings of one family, in a repeated-measures design, using a 'robust cluster' command to estimate standard errors (Tye et al., 2012; Wood et al., 2009). This command was not available for correlational analyses, which were conducted to investigate the effect of age on EEG spectral power in the full sample. For these analyses siblings were removed from the ADHD (n=6), preterm (n=25) and control group (n=69) of the full sample. Post-hoc analyses were carried out using the independent samples t-tests for between-subjects contrasts, and paired samples t-tests for within-individual task-related differences in condition (EO and CPT-OX) and electrode site by employing the 'cltest' command (Herrin, 2012) to control for the non-independence of the data. Bonferroni correction was implemented to correct for multiple testing in the different frequency bands: Bonferroni adjusted p-value=0.0125. Effect size (Cohen's d), which was calculated using the difference in the means divided by the pooled standard deviation, is also reported (Cohen, 1988). According to Cohen (1988), d=0.20 constitutes a small effect, d=0.50 a medium effect and d=0.80 a large effect.

In full sample analyses, age was routinely included as a covariate since the groups differed significantly on age. In the full sample, groups further differed in terms of IQ. Therefore, all analyses in the full sample were subsequently re-ran with IQ as a covariate, but results and significant levels did not change. In the age-matched subsample age was not included as a covariate since all three groups were matched on age. Although the groups in both the full sample and the age-matched subsample differed significantly on gender, gender was not included as a covariate in the group analyses to avoid controlling for ADHD status (Cheung et al., 2015a).



### 3.4 Results

#### 3.4.1 Full sample

##### 3.4.1.1 QEEG results

The random intercept model indicated no significant main effects of group in the delta ( $z=0.08$ ,  $p=0.938$ ), theta ( $z=0.05$ ,  $p=0.959$ ), alpha ( $z=-0.10$ ,  $p=0.920$ ) or beta frequency ranges ( $z=-0.48$ ,  $p=0.632$ ).

Significant main effects of condition emerged for both delta ( $z=6.84$ ,  $p<0.001$ ) and theta power ( $z=10.63$ ,  $p<0.001$ ). No significant main effects of condition were found for alpha ( $z=0.59$ ,  $p=0.556$ ) and beta power ( $z=1.77$ ,  $p=0.077$ ). Post-hoc paired sample t-tests revealed that, overall, both delta ( $t=-6.71$ ,  $df=372$ ,  $p<0.001$ ) and theta power ( $t=-12.07$ ,  $df=372$ ,  $p<0.001$ ) were significantly reduced during EO compared to CPT-OX.

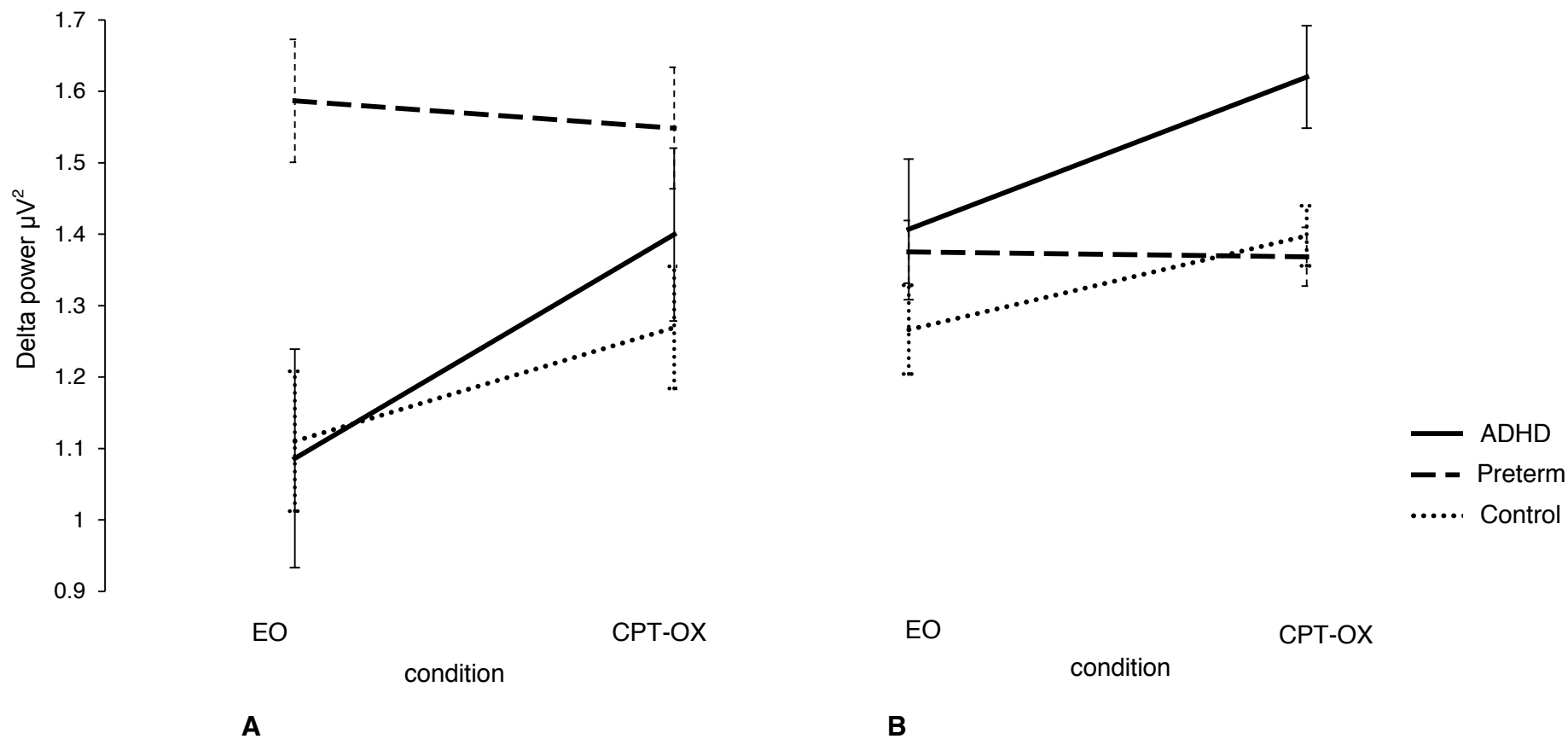
The random intercept model yielded a significant group-by-condition interaction for delta power ( $z=-3.86$ ,  $p<0.001$ ) (Figure 3.1A). No significant group-by-condition interactions were found for theta ( $z=-1.25$ ,  $p=0.213$ ), alpha ( $z=-1.19$ ,  $p=0.234$ ) and beta power ( $z=-2.25$ ,  $p=0.024$ ). Post-hoc independent sample t-tests revealed that delta power in individuals with ADHD was not significantly different from controls during EO ( $t=0.27$ ,  $df=139$ ,  $p=0.788$ ) or CPT-OX ( $t=-1.73$ ,  $df=139$ ,  $p=0.086$ ). While the ADHD group showed significantly reduced delta power compared to the preterm group during EO ( $t=-5.83$ ,  $df=175$ ,  $p<0.001$ ), with large effect size ( $d=0.92$ ), during CPT-OX the ADHD and preterm groups did not differ significantly with regard to delta power ( $t=-1.91$ ,  $df=178$ ,  $p=0.058$ ). The preterm group showed significantly increased delta power compared to the control group during EO ( $t=-6.85$ ,  $df=178$ ,  $p<0.001$ ) and CPT-OX ( $t=-4.28$ ,  $df=178$ ,  $p<0.001$ ), with large ( $d=0.95$ ) and moderate ( $d=0.60$ ) effect sizes respectively. Paired sample t-tests demonstrated an increase in delta power from EO to CPT-OX in the ADHD ( $t=-7.46$ ,  $df=74$ ,  $p<0.001$ ) and control groups ( $t=-5.35$ ,  $df=153$ ,  $p<0.001$ ). No significant change from EO to CPT-OX was found in the preterm group ( $t=0.343$ ,  $df=144$ ,  $p=0.732$ ) (Figure 3.1A).

Significant main effects of recording site (frontal, central and parietal) emerged for theta ( $z=4.51$ ,  $p<0.001$ ) and alpha power ( $z=19.68$ ,  $p<0.001$ ) but not for

delta ( $z=-0.69$ ,  $p=0.490$ ) and beta power ( $z=0.37$ ,  $p=0.713$ ). Since no significant main effect of recording site was found for delta power, post-hoc results are not presented here.

#### *3.4.1.2 Correlation results*

Correlational analyses were conducted to investigate the effect of age on delta power. Results for the other frequency bands are not presented here, since delta was the only frequency range to demonstrate a significant group-by-condition interaction. Significant negative correlations emerged between age and delta power during EO ( $r=-0.62$ ,  $p<0.001$ ;  $r=-0.50$ ,  $p<0.001$ ;  $r=-0.57$ ,  $p<0.001$ ) and CPT-OX ( $r=-0.64$ ,  $p<0.001$ ;  $r=-0.60$ ,  $p<0.001$ ;  $r=-0.53$ ,  $p<0.001$ ) in the ADHD, preterm and control groups respectively, highlighting the importance of additional analyses on more closely age-matched groups.



**Figure 3.1. Mean delta power across resting-state (EO) and task (CPT-OX) condition in (A) the full sample and (B) the age-matched adolescent subsample. Error bars represent 95% confidence intervals.**

### **3.4.2 Age-matched subsample**

#### **3.4.2.1 QEEG results**

The random intercept model indicated no significant main effects of group in the delta ( $z=-0.79$ ,  $p=0.427$ ), theta ( $z=-0.37$ ,  $p=0.708$ ), alpha ( $z=-0.26$ ,  $p=0.793$ ) or beta frequency ranges ( $z=-0.15$ ,  $p=0.881$ ).

Significant main effects of condition emerged for both delta ( $z=3.65$ ,  $p<0.001$ ) and theta power ( $z=8.08$ ,  $p<0.001$ ). No significant main effects of condition were found for alpha ( $z=-0.76$ ,  $p=0.445$ ) and beta power ( $z=-0.04$ ,  $p=0.966$ ). Post-hoc paired sample t-tests revealed that, overall, both delta ( $t=-3.56$ ,  $df=192$ ,  $p<0.001$ ) and theta power ( $t=-8.61$ ,  $df=192$ ,  $p<0.001$ ) were significantly reduced during EO compared to CPT-OX.

A significant group-by-condition interaction emerged for delta power ( $z=-3.37$ ,  $p<0.001$ ) (Figure 3.1B). No significant group-by-condition interactions were found for theta ( $z=-1.43$ ,  $p=0.152$ ), alpha ( $z=-2.34$ ,  $p=0.020$ ) and beta power ( $z=-2.54$ ,  $p=0.016$ ). Post-hoc independent sample t-tests revealed that delta power during EO was not significantly different in individuals with ADHD compared to control ( $t=-1.27$ ,  $df=84$ ,  $p=0.26$ ; Cohen's  $d=0.26$ ) or preterm-born individuals ( $t=0.15$ ,  $df=113$ ,  $p=0.881$ ; Cohen's  $d=0.03$ ). However, during CPT-OX the ADHD group showed significantly greater delta power than both the control ( $t=-2.86$ ,  $df=84$ ,  $p=0.005$ ) and preterm groups ( $t=3.41$ ,  $df=113$ ,  $p<0.001$ ), with moderate ( $d=0.61$ ) and moderate-to-large ( $d=0.71$ ) effect sizes respectively. The preterm group did not differ significantly from the control group with regard to delta power during EO ( $t=-1.58$ ,  $df=133$ ,  $p=0.117$ ) or CPT-OX ( $t=0.80$ ,  $df=133$ ,  $p=0.423$ ). Paired sample t-tests demonstrated an increase in delta power from EO to CPT-OX in the ADHD ( $t=-4.33$ ,  $df=35$ ,  $p<0.001$ ) and control groups ( $t=-3.26$ ,  $df=62$ ,  $p=0.002$ ). No significant change from EO to CPT-OX was found in the preterm group ( $t=0.240$ ,  $df=93$ ,  $p=0.811$ ) (Figure 3.1B).

Moreover, significant main effects of recording site (frontal, central and parietal) were found for theta ( $z=3.92$ ,  $p<0.001$ ) and alpha power ( $z=16.90$ ,  $p<0.001$ ), but not for delta ( $z=-0.42$ ,  $p=0.675$ ) and beta power ( $z=0.82$ ,  $p=0.410$ ). Since no

significant main effect of recording site emerged for delta power, post-hoc results are not presented here.

### **3.5 Discussion**

In this study examining the relationship of EEG spectral power in adolescents with ADHD, adolescents born preterm and control adolescents across resting-state and cognitive task conditions, different cortical activation patterns in the delta band emerged for the three groups. Since we demonstrated considerable age effects on delta power, the following discussion of results on group differences is based on the age-matched subsample. While the ADHD group did not differ significantly from the preterm and control groups during EO with regard to delta power, during CPT-OX the ADHD group showed significantly increased delta power compared to both the preterm and control groups. The preterm group did not differ significantly from the control group with regard to delta power during EO or CPT-OX.

Rest-to-task transition effects differed between the ADHD and the preterm group in the delta band. While the preterm group showed no changes in EEG spectral power from resting-state to task condition, the ADHD group exhibited a task-related increase in delta power. As a result, the ADHD and preterm groups did not differ with regard to delta power during the resting-state condition, but participants with ADHD demonstrated significantly increased delta power compared to the preterm group during the cognitive task condition. To date, no study has directly compared the cortical activity patterns of individuals with ADHD and preterm-born individuals. These findings provide evidence for differences in oscillation patterns in the delta range, especially with regard to rest-to-task transition effects, between adolescents with ADHD and adolescents born preterm.

Both the ADHD and control groups showed a task-related increase in delta power from resting-state to task condition. Whereas delta power did not differ significantly between these two groups during the resting-state condition, power in the delta band was significantly increased in the ADHD group compared to controls during the cognitive task condition. This result of rest-to-task transition

effects in the ADHD and control groups does not replicate previous research in men (Skirrow et al., 2015) and women (chapter 2) with adult ADHD, which found no theta power differences in cortical activation between controls and individuals with ADHD during the CPT-OX and no change in EEG spectral power from resting-state to cognitive task in the ADHD group. In addition, the findings of a lack of significant differences between these two groups during the resting-state condition fail to replicate the previously reported elevation of slow oscillatory power during rest in individuals with ADHD (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke et al., 2003a, 2006, 2008; Koehler et al., 2009; Snyder & Hall, 2006). However, they are in agreement with more recent studies failing to replicate slow oscillatory power abnormalities in children, adolescents and adults with ADHD compared to controls during resting-state (Buyck & Wiersema, 2014; Kitsune et al., 2015; Liechti et al., 2013; Loo et al., 2009; Ogrim et al., 2012; Poil et al., 2014).

While it is conceivable that heterogeneity in the ADHD samples with regard to ADHD subtype (Buyck & Wiersema, 2014; Clarke et al., 2001; Loo et al., 2013), medication status (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002; Clarke et al., 2003b; Loo, Hopfer, Teale, & Reite, 2004) and comorbidities (Clarke, Barry, McCarthy, & Selikowitz, 2002; Loo et al., 2013) have resulted in inconsistencies between studies, it seems more likely that differences in sample ages may have contributed to the discrepancies between the current findings in adolescents and previous findings in adults with ADHD (chapter 2; Skirrow et al., 2015). This idea is supported by our findings of a negative moderate-to-large relationship between delta power and age across all three groups in the full sample, which suggest substantial maturational effects on delta power. Differences in results between the full sample and the age-matched subsample further suggest maturational effects on delta power. Compared to the preterm group of the age-matched subsample, the preterm group in the full sample showed increased delta power during both EO and CPT-OX. These findings point to age effects because the preterm group in the full sample is younger, on average, than the preterm group of the age-matched subsample, and power in slow (delta and theta) frequency bands decreases across the lifespan (Clarke et al., 2001; Gasser, Verleger, et al., 1988; John et al., 1980; Matoušek & Petersén, 1973; Somsen et al., 1997).

That EEG spectral power in all frequency bands is affected by age has also been shown in other studies of individuals with ADHD (Buyck & Wiersema, 2014; Liechti et al., 2013; Monastra et al., 2001). Research further indicates the possibility that developmental trajectories of EEG spectral power in individuals with ADHD may not be linear throughout the lifespan but may deviate in late childhood (Liechti et al., 2013) or adulthood (Poil et al., 2014). Consequently, discrepancies between our current and previous findings may arise from differences in sample ages. Yet, longitudinal studies are needed to fully elucidate the trajectory of EEG spectral power development in ADHD and to examine these discrepancies in rest-to-task transition effects in ADHD.

The increase in delta power from rest to cognitive task condition in adolescents with ADHD and control adolescents may be linked to the increased task demand (Harmony, 2013; Lal & Craig, 2001) and enhanced task performance (Knyazev, 2012). It is plausible that elevated delta power during the cognitive task condition in adolescents with ADHD compared to controls indicates a compensatory mechanism (Lenartowicz et al., 2014). Yet, this possibility remains to be elucidated in future studies employing tools such as independent component analysis (ICA) and time-frequency analysis to tease apart the various cognitive processes involved in task performance.

The preterm group showed no differences in delta power during resting-state and cognitive task conditions compared to controls. While delta power significantly increased in control individuals from the rest condition to the task condition, no change in delta power from EO to CPT-OX was seen in the preterm group. This seeming lack of task-dependent modulation of delta power in preterm participants may result from lack of task engagement. This cannot be ruled out, as causal models (or the direction of effect) were not tested directly. Yet, the participants overtly displaying a lack of task engagement, as highlighted by excessive error counts, were excluded from the analysis. Covert task disengagement, where individuals born preterm seem to be on task but experience a drift of attention, could, nevertheless, result in decreased cortical activity. Future research is needed to replicate and elucidate the lack of rest-to-task transition effects in adolescents born preterm.

A few limitations should be considered along with the present results. Our sample of individuals born preterm was drawn from the general population and may differ from samples ascertained through clinics or support groups. Yet, a general population sample reduces the risk of referral and selection biases associated with clinical samples. As reflected in its above-average IQ, our control sample may not be fully representative of other typically developing adolescents. Another limitation of this study is that we examined cortical activation for the frequency bands alpha, beta, delta and theta. While some researchers have advocated abandoning fixed frequency bands (Klimesch, 1999), the grouping of these frequencies into the particular bands has occurred historically and makes comparison between studies easier. Moreover, QEEG provides averaged measures of cortical activation across the resting-state and the cognitive task condition. To explore the various cognitive processes underlying cortical activation, future research may employ time-frequency analysis. For finer resolution and increased signal to noise ratio, future studies may further conduct source based analyses such as ICA.

In conclusion, our results provide some of the first QEEG evidence for differences in oscillation patterns in the delta range, especially with regard to rest-to-task transition effects between term-born adolescents with ADHD and adolescents born preterm. Furthermore, our data indicate an important effect of age on EEG spectral power. Future large-scale studies are needed to elucidate how the cortical activation patterns observed in adolescents born preterm mediate cognitive impairments and clinical symptoms. To fully elucidate the discrepancies in rest-to-task transition effects between this and previous studies longitudinal studies of the trajectory of EEG spectral power development in ADHD are needed.



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## Chapter 4. Neurophysiological impairments of attention and inhibition: a comparison of adolescents with ADHD and adolescents born preterm

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### 4.1 Abstract

**Background.** Preterm birth has been associated with an increased risk for ADHD-like symptoms and cognitive impairments similar to those seen in ADHD, including attention and inhibitory control difficulties. Yet, data on direct comparisons across ADHD and preterm birth on cognitive-neurophysiological measures are limited. **Methods.** First, we directly compared 75 term-born adolescents with ADHD, 145 adolescents born preterm and 153 term-born control adolescents on cognitive-performance and event-related potential (ERP) measures associated with attentional and inhibitory processing from a cued continuous performance test (CPT-OX) to elucidate whether the ADHD-like symptoms and cognitive impairments in individuals born preterm reflect identical cognitive–neurophysiological impairments in term-born individuals with ADHD. Although age was statistically controlled in the analysis, we reran all analyses on a carefully age-matched subsample due to significant group mean differences in age and the possibility of strong age effects on ERP measures. This sub-sample comprised 36 term-born adolescents with ADHD, 94 preterm-born and 63 control adolescents. **Results.** As demonstrated by differences in results between the full sample and the age-matched subsample, age had an effect on ERP measures. We, therefore, interpreted the group comparisons from the carefully age-matched analyses only. Go-P3 amplitude was reduced, reflecting impaired response execution, in preterm-born adolescents compared to both control adolescents and adolescents with ADHD. Moreover, in adolescents born preterm CNV amplitude was attenuated, reflecting impairments in response preparation, compared to controls but not compared to adolescents with ADHD. The preterm group demonstrated significantly reduced NoGo-P3 amplitude, reflecting impaired response inhibition, compared to the control group at Cz but the two groups did not differ significantly at FCz. The preterm group further showed significantly increased NoGo-P3 amplitude compared to the ADHD group at FCz but not at Cz. Compared to the control group, NoGo-P3 amplitude was attenuated in the ADHD group at Cz but not at

FCz. **Conclusion.** These findings indicate impairments in response preparation, response execution and response inhibition in adolescents born preterm. While the response inhibition impairments found in adolescents born preterm overlap with those found in term-born adolescents with ADHD, the preterm group also shows unique deficits, suggesting more wide-ranging deficits in the preterm group compared to the ADHD group.

## 4.2 Introduction

Preterm birth has been associated with an increased risk for ADHD-like symptoms and cognitive impairments similar to those seen in ADHD, including attention and inhibitory control difficulties (Aarnoudse-Moens et al., 2009; Anderson et al., 2011; Geva & Feldman, 2008; Lawrence et al., 2009; Miskovic et al., 2009; Mulder et al., 2009; Nosarti et al., 2006; Wilson-Ching et al., 2013). Direct comparisons across ADHD and preterm birth, using identical measures, may elucidate whether the ADHD-like symptoms and cognitive impairments in preterm-born individuals reflect identical cognitive–neurophysiological impairments in term-born individuals with ADHD.

Cognitive performance data alone provides only indirect insight into covert processing as various covert mechanisms may result in indistinguishable overt performance on cognitive tasks, and abnormal covert processing may underlie overt performance deficits or normal performance (Banaschewski & Brandeis, 2007). The study of event-related potentials (ERPs), however, allows direct investigation of these covert brain processes with millisecond temporal resolution (see section 1.5.3.2. for discussion). Consequently, ERP measures may permit a sensitive comparison of the cognitive-neurophysiological profiles associated with ADHD and preterm birth (McLoughlin, Makeig, & Tsuang, 2014).

Impairments in attentional processing and response inhibition in ADHD have frequently been examined using ERP components obtained from the cued continuous performance test (CPT-OX). The CPT-OX comprises the presentation of cue ('XOX'), target (Go; target 'OXO' preceded by a cue 'XOX') and non-target stimuli (NoGo; letters other than 'OXO' following a cue 'XOX') and entails a response to a target stimulus preceded by a cue (van Leeuwen et al., 1998). The CPT-OX yields electrophysiological indices of attentional orienting (Cue-P3) and response preparation (contingent negative variation; CNV) during the presentation of cue stimuli, electrophysiological indices of response execution (Go-P3) during Go trials, as well as electrophysiological indices of conflict monitoring (NoGo-N2) and response inhibition (NoGo-P3) during NoGo trials (Tye et al., 2011).

The fronto-central NoGo-P3, the third positive waveform following NoGo trials, has consistently shown reduced amplitude in children, adolescents and adults with ADHD (Albrecht et al., 2013; Banaschewski et al., 2003; Brandeis, Banaschewski, et al., 2002; Dhar et al., 2010; Doehnert et al., 2010; Fallgatter et al., 2004, 2005; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011; Tye, Asherson, et al., 2014; Valko et al., 2009; van Leeuwen et al., 1998). Reduced amplitude of the parietal Cue-P3, as well as attenuated CNV amplitude, which is a late negative potential before the presentation of the next stimulus, have also been demonstrated in children, adolescents and adults with ADHD (Albrecht et al., 2013; Doehnert et al., 2010; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011; Tye, Asherson, et al., 2014). However, not all studies have replicated these findings (Dhar et al., 2010). Few studies have directly investigated Go-P3 amplitude in individuals with ADHD and findings are inconsistent. Some studies report attenuated Go-P3 amplitude (Strandburg et al. 1996; Overtom et al. 1998; Banaschewski et al. 2004; Lawrence et al. 2005), while others show no case-control differences (Albrecht et al., 2013; Banaschewski et al., 2003; McLoughlin et al., 2010; van Leeuwen et al., 1998). Lastly, although conflict-monitoring deficits, indexed by attenuated amplitude of the frontally distributed N2, have been found in ADHD during high-conflict tasks, such as the flanker task (Albrecht et al., 2008; Gow et al., 2012; Johnstone et al., 2009; McLoughlin et al., 2009), case-control differences in N2 amplitude to non-target stimuli (NoGo-N2) are typically not found in the CPT-OX (McLoughlin et al., 2010; Yeung & Cohen, 2006). One study investigating ADHD case-control differences on data partially overlapping with the current analysis reported attenuated amplitude of the CNV, Cue-P3 and NoGo-P3 in adolescents with ADHD compared to control adolescents (Cheung et al., 2015a).

While the neurophysiology of preterm-born infants in neonatal intensive care units (Meijer et al., 2014; Victor et al., 2005) and in the postnatal period (Beckwith & Parmelee, 1986; Duffy et al., 1990; González et al., 2011; Hayakawa et al., 2001; Vecchierini et al., 2007) are well researched, few ERP studies have been conducted in children, adolescents or adults born preterm. In auditory ERP studies, preterm-born children have demonstrated abnormalities in early sensory and attentional ERP components (mismatch negativity (MMN),

P1 and P3a) (Hövel et al., 2014; Mikkola et al., 2007, 2010). Larger N2 amplitudes have also been found in 5-year-old children born very preterm (<32 weeks) (Hövel et al., 2014; Mikkola et al., 2007). Despite initial evidence for impairments in ERP measures of attentional processing in preterm-born individuals, the research overall is limited. Moreover, no ERP study to date has investigated impairments in attentional processing and response inhibition in preterm-born individuals using the CPT-OX. Yet, the CPT-OX is a sensitive measure of the cognitive impairments seen in ADHD and preterm-born individuals are at increased risk for cognitive impairments similar to those linked to ADHD, including attention and inhibitory control difficulties (Aarnoudse-Moens et al., 2009; Anderson et al., 2011; Geva & Feldman, 2008; Lawrence et al., 2009; Miskovic et al., 2009; Mulder et al., 2009; Nosarti et al., 2006; Wilson-Ching et al., 2013).

Direct comparisons on ERP measures in ADHD and preterm birth are scarce. One ERP study investigated attentional processing in very low birth weight children born preterm (<1501g and <34 weeks) with and without ADHD, as well as in term-born controls and term-born individuals with ADHD (Potgieter et al., 2003). Term- and preterm-born children with ADHD, who showed increased mean reaction time (MRT) and reaction time variability (RTV), and who made more commission and omission errors on a visual oddball paradigm, also demonstrated an increased NoGo-N2 amplitude compared to term-born controls and preterm-born participants without ADHD. However, the sample size was small (N=41) and the test battery was restricted to a visual oddball task. No study to date has compared ERP components associated with attentional and inhibitory processing in both ADHD and preterm birth using the CPT-OX. In addition, despite major advances in neonatal care over the last few decades (Goldenberg et al. 2008), and the resulting possibility to study survivors of preterm birth, cognitive-performance and ERP measures remain to be assessed in adolescents born preterm.

In the current study, we aim to directly compare cognitive-performance and ERP measures associated with attentional and inhibitory processing in adolescents with ADHD and adolescents born preterm, to establish whether the cognitive impairments associated with preterm birth, including attention and

inhibitory control difficulties, reflect identical neurophysiological impairments to those observed in term-born individuals with ADHD. Although the full sample consists entirely of adolescents, significant differences in age emerge between the groups (Table 4.1). To address this issue, age is controlled statistically in the analysis of the full sample. In addition, all analyses are rerun using a carefully age-matched subsample. If diverging results in the age-matched subsample emerge, the findings from the age-matched subsample, rather than from the full sample, are discussed and interpreted because of apparent age effects. We further aim to explore the effect of age on ERP measures within these three groups of the full sample using correlation analyses.

## **4.3 Method**

### ***4.3.1 Sample***

ADHD and control sibling pairs who had taken part in previous research (Chen et al., 2008; Kuntsi et al., 2010; Wood, Asherson, Rijdsdijk, & Kuntsi, 2009), were invited to take part in a follow-up study (Cheung et al., 2015a, 2015b). All participants were of European Caucasian descent and had one or more full siblings available for ascertainment. Initially, participants with ADHD were included if they had a clinical diagnosis of DSM-IV combined-type ADHD during childhood. At follow-up, participants in the ADHD group were included if, as well as having an ADHD diagnosis in childhood, they met DSM-IV criteria for any ADHD subtype at follow-up. The control group was initially recruited from primary (ages 6–11 years) and secondary (ages 12–18 years) schools in the UK, aiming for an age- and sex-match with the ADHD sample. Control individuals were included in the study if they did not meet DSM-IV criteria for any ADHD subtype either in childhood or at follow-up. Exclusion criteria for both groups included IQ<70, autism, epilepsy, general learning difficulties, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD.

We followed up the sample on average 5.8 years (SD=1.1) after initial assessments. Siblings of individuals with ADHD were included in the ADHD group if they met DSM-IV criteria for any ADHD subtype at follow-up. Siblings of

control individuals were included in the control group if they did not meet DSM-IV criteria for any ADHD subtype at follow-up. The ADHD and control groups were previously included in a study investigating ADHD case-control differences on cognitive and neurophysiological markers of ADHD persistence and remission (Cheung et al., 2015a). While ADHD-control differences for this sample have been reported previously, here, a subsample of the ADHD and control groups is compared to a group of preterm-born adolescents.

At follow-up, six participants from the ADHD-sibling pair sample were excluded from the group analyses, as they had missing parent ratings of clinical impairment and their current ADHD status could not be determined. Two additional participants from the ADHD-sibling pair sample were excluded because they became very drowsy during the cognitive task and fell asleep. In two cases there was EEG equipment failure, resulting in the exclusion. Seven participants from the ADHD-sibling pair sample, who were born preterm, as well as 38 individuals from the ADHD-sibling pair sample, who provided no information about gestational age (GA), were also excluded. Two participants with childhood ADHD, who did not meet ADHD symptom criteria but met clinical levels of impairment at follow-up, were further excluded to minimize heterogeneity in the ADHD sample.

Since age has an effect on ERP measures (Doehnert et al., 2010, 2013; Fallgatter, Mueller, & Strik, 1999; Zurrón, Lindín, Galdo-Alvarez, & Díaz, 2014)., we chose to also analyse a homogeneous group of participants with regard to age. For this subsample, we excluded an additional 37 individuals from the ADHD-sibling pair sample who fell outside the investigated age range (14-19 years). On average, the ADHD group was older than the preterm group.

Forty-five participants from the control-sibling pair sample were excluded because no GA information was available. Six control participants were removed from the analyses for meeting DSM-IV ADHD criteria based on the parent-rated Barkley Informant Rating Scale (Barkley & Murphy, 2006). For the subsample analysis, an additional 66 participants from the control-sibling pair sample were excluded because they fell outside the investigated age range (14-19 years). On average, the control group was older than the preterm group.

The preterm group was recruited from secondary schools in Southeast England. All preterm participants had one or more full siblings available for ascertainment, and were born before 37 weeks' gestation. Siblings of individuals born preterm were included in the preterm group if they were born before 37 weeks' gestation. Exclusion criteria for the preterm group included IQ<70, general learning difficulties, cerebral palsy and any other medical conditions that affects motor co-ordination including epilepsy. Three individuals born preterm were excluded because they showed insufficient understanding/engagement with the CPT-OX, as suggested by the testing notes and further indicated by extreme omission errors=17, 31 and 41 respectively, which were more than 3.5 SD from the mean (Tye et al., 2011; Tye, Asherson, et al., 2014). Seven individuals from the preterm-sibling pair sample were excluded because their GA was equal to or above 37 weeks; one individual was excluded because of an IQ<70 and 26 participants had to be excluded due to EEG equipment failure. For the subsample analysis, an additional 71 individuals from the preterm-sibling pair sample were excluded because they fell outside the investigated age range (14-19 years). On average, the preterm group was younger than the ADHD and control groups. Seven preterm-born individuals in the full sample and three preterm-born individuals in the age-matched subsample met diagnostic criteria for a research diagnosis of ADHD. Since, in this thesis, preterm birth is investigated as a potential risk factor for ADHD, individuals who were born preterm and also demonstrate high levels of ADHD symptoms are not excluded from this analysis.

The final full sample consisted of 75 ADHD participants (six sibling pairs and 63 singletons), 145 preterm-born participants (25 sibling pairs and 95 singletons) and 153 controls (69 sibling pairs and 15 singletons). The groups differed significantly in terms of age, IQ, gender distribution, GA and ADHD symptom scores (Table 4.1). As reported in chapter 3, the ADHD group showed significantly higher ADHD symptom scores than both the preterm ( $t=19.57$ ,  $df=175$ ,  $p<0.001$ ) and control groups ( $t=-46.19$ ,  $df=139$ ,  $p<0.001$ ). The preterm group further demonstrated significantly higher ADHD symptom scores than the control group ( $t=-8.85$ ,  $df=178$ ,  $p<0.001$ ). Age was included as a covariate in all analyses. All analyses were rerun with IQ as an additional covariate. Gender



was not included as a covariate in the group analyses to avoid controlling for ADHD status (Cheung et al., 2015a). Written informed consent was obtained and the studies were approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58) and the National Research Ethics Service Committee London – Bromley (13/LO/0068).

**Table 4.1. Descriptive statistics.**

	<b>ADHD</b>	<b>Preterm</b>	<b>Control</b>	<b>Statistic</b>	<b>P-value</b>
<b><i>Full sample</i></b>	n=75	n=145	n=153	-	-
<b>GA in weeks (SD)</b>	39.9 (1.4)	33.2 (2.8)	40.0 (1.2)	z=-19.9	<0.001
<b>IQ (SD)</b>	97.1(13.7)	104.2 (12.5)	110.3 (12.5)	z=-2.4	0.015
<b>Age (SD)</b>	18.5 (2.9)	15.3 (1.9)	17.8 (2.1)	z=-8.1	<0.001
<b>Age range</b>	12.7-25.9	11.0-20.0	11.9-21.6	-	-
<b>Males %</b>	86.7	51.0	75.6	$\chi^2=34.4$	<0.001
<b>ADHD symptom score</b>	14.0 (3.0)	3.6 (4.0)	0.0 (0.0)	t= 6.3	<0.001
<b><i>Age-matched subsample</i></b>	n=36	n=94	n=63	-	-
<b>GA in weeks (SD)</b>	39.72 (1.3)	33.5 (2.4)	40.0 (1.10)	z=-18.0	<0.001
<b>IQ (SD)</b>	96.4 (14.0)	103.6 (13.2)	108.0 (12.4)	z=-1.6	0.112
<b>Age (SD)</b>	16.6 (1.5)	16.4 (1.1)	16.7 (1.0)	z=-1.7	0.082
<b>Age range</b>	14.1-18.9	14.8-18.8	14.4-18.1	-	-
<b>Males %</b>	88.9	44.7	47.5	$\chi^2=24.1$	<0.001
<b>ADHD symptom score</b>	14.2 (3.0)	3.5 (3.8)	0.0 (0.0)	t= 3.4	<0.001

The final age-matched subsample consisted of 36 ADHD participants (five sibling pairs and 26 singletons), 94 preterm-born participants (13 sibling pairs and 68 singletons) and 63 controls (eight sibling pairs and 47 singletons). The groups did not differ in terms of age or IQ (Table 4.1). Significant differences in gender distribution, GA and ADHD symptom scores were observed. As reported in chapter 3, the ADHD group showed significantly higher ADHD symptom

scores than both the preterm ( $t=14.62$ ,  $df=113$ ,  $p<0.001$ ) and the control groups ( $t=-35.25$ ,  $df=84$ ,  $p<0.001$ ). The preterm group further demonstrated significantly higher ADHD symptom scores than the control group ( $t=-6.72$ ,  $df=133$ ,  $p<0.001$ ). Gender was not included as a covariate in the group analyses to avoid controlling for ADHD status (Cheung et al., 2015a).

### **4.3.2 Procedure**

Participants attended a single 4.5 h research session, which included an EEG assessment, an IQ test and clinical interviews. As part of the EEG assessment, participants completed a CPT with flankers (CPT-OX) (Doehnert et al., 2010; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011). The task was preceded by two 3-minute resting-state recordings and was the first of three cognitive-EEG tasks to be conducted during the testing session. Participants were requested to remain as still as possible, and keep their eyes on a fixed point in front of them for the duration of the recording. A 48 h ADHD medication-free period was required before the research session.

### **4.3.3 Measures**

#### **4.3.3.1 ADHD diagnosis**

In the ADHD group, ADHD was assessed using parental ADHD symptom ratings on the Diagnostic Interview for ADHD in adults (DIVA) (Kooij & Francken, 2007) and the Barkley's functional impairment scale (BFIS) (Barkley & Murphy, 2006). The DIVA is a semi-structured interview designed to evaluate the DSM-IV criteria for both adult and childhood ADHD symptoms and impairment. It consists of 18 items used to define the DSM-IV symptom criteria for ADHD. Each item is scored affirmatively if the behavioural symptom was present *often* within the past six months. Based on DSM-IV criteria, a research diagnosis of ADHD was made if participants scored six or more on either the inattention or hyperactivity-impulsivity subscales of the DIVA and if they received two or more positive scores on two or more areas of impairment on the BFIS. In the preterm group, ADHD was assessed using parental ADHD symptom ratings on the DIVA (Kooij & Francken, 2007). A research diagnosis of

ADHD was made if participants scored six or more on the inattention or hyperactivity-impulsivity subscales of the DIVA.

#### *4.3.3.2 IQ*

The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV) (Wechsler, 1999) were administered to all participants to derive an estimate of IQ.

#### *4.3.3.3 Cued continuous performance task with flankers*

The CPT-OX is a cued Go/NoGo task that probes attention, preparation and response inhibition. The task consisted of 400 black letter arrays, made up of a centre letter and incompatible flankers on each side to increase difficulty. The presented arrays included the cue letter 'O', the target letter 'X' as well as the distractors 'H', 'B', 'C', 'D', 'E', 'F', 'G', 'J' and 'L'. Letters were presented centrally on the computer monitor, subtending approximately 5°. Cue and target letters ('O' and 'X' respectively) were flanked by incompatible letters ('XOX' and 'OXO' respectively). Participants were instructed to ignore the flanking letters and respond as quickly as possible to cue-target sequences ('O'-'X'). 80 cues ('XOX') were followed by the target ('OXO') in 40 trials (Go condition), and by neutral distractors in the remainder of trials (NoGo condition). On 40 trials, the target letter 'X' was not preceded by a cue 'O' and had to be ignored. Letters were presented every 1.65 s for 150 ms in a pseudo-randomised order. Ten practice trials preceded the main task and were repeated, if required, to ensure participant comprehension. Participants were instructed to respond only to Cue-Go sequences by pressing a button as quickly as possible with the index finger of their preferred hand. Participants were further asked to withhold the response in the presence of a NoGo stimulus, in the presence of a Go stimulus not preceded by a cue, or in the presence of any other irrelevant letters. Task duration was 11 min.

Cognitive-performance measures obtained from the CPT-OX included target MRT (i.e. mean latency of responding in milliseconds after target onset), RTV (measured as standard deviation of target reaction time) and number of errors. MRT and RTV were obtained from correct Go trials. Errors included total

omission errors (non-responses to Go trials) and total commission errors (responses to Cue, NoGo or distractor stimuli).

#### ***4.3.4 Electrophysiological recording and analysis***

The EEG was recorded from a 62 channel direct-current-coupled recording system (extended 10–20 montage), using a 500 Hz sampling-rate, impedances under 10 k $\Omega$ , and FCz as the recording reference. The electro-oculograms were recorded from electrodes above and below the left eye and at the outer canthi. The EEG data were analysed using Brain Vision Analyzer 2.0 (Brain Products, Germany). Researchers were blind to group status during EEG pre-processing and analysis. Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and digitally filtered using Butterworth band-pass filters (0.1-30 Hz, 24 dB/oct). All trials were also visually inspected for electrical artefacts (due to electrical noise in the EEG recording) or obvious movement, and sections of data containing artefacts were removed manually. Ocular artefacts, corresponding to blink-related and vertical and horizontal eye movements, were identified using the infomax Independent Component Analysis (ICA) algorithm (Jung et al., 2000), which allows for removal of the components associated with ocular artefacts by back-projection of all but those components. Sections of data with remaining artefacts exceeding  $\pm 100 \mu\text{V}$  in any channel or with a voltage step greater than  $50 \mu\text{V}$  were automatically rejected.

For the CPT, stimulus-locked epochs (stimulus window from –200 to 1650 ms) were averaged based on three different response conditions: Cue, Go and NoGo. Averages were calculated for trials with correct responses (Go) or correctly rejected trials (NoGo and Cue), which included at least 20 clean segments. Based on previous research (Albrecht et al., 2013; Doehnert et al., 2013; McLoughlin et al., 2010), ERP measures were identified within selected electrodes and latency windows for which effects were expected to be largest. These measures were then confirmed separately for the three groups using topographic maps.

ERPs were measured as the mean amplitude in a given latency window. In Cue trials, the P3 was measured at Pz between 300-650 ms, and the CNV was measured at Cz between 1300-1650 ms. In Go trials, the P3 was measured at Pz between 250-500 ms. No clear N2 was observed in Go trials, consistent with other studies employing tasks with low conflict-monitoring demands (Bokura, Yamaguchi, & Kobayashi, 2001; Gajewski & Falkenstein, 2013) and was, therefore, not included in the analysis. In NoGo trials, the P3 was measured at Cz and FCz between 250-550 ms and the N2 was measured at Fz between 175-325 ms.

Whereas ERP components with baseline correction are thought to represent the absolute change in neural activity elicited by the stimulus, ERP components without baseline correction are thought to reflect the absolute state of neural activity measured at a given time (Brandeis & Lehmann, 1986). Here, results are presented and interpreted without baseline correction since most previous ERP analyses on CPT-OX did not apply a baseline correction (Albrecht et al., 2013; Banaschewski et al., 2004; Doehnert et al., 2013; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011), including the study partially overlapping with the current analysis (Cheung et al., 2015a). Moreover, there is evidence to suggest that this approach may distort post-stimulus topographies (Brandeis & Lehmann, 1986; Koenig & Gianotti, 2009). However, to enable comparison to analyses where such corrections have been applied, and to explore whether our results change, analyses were rerun with baseline correction in the age-matched sample (see Appendix 2).

#### ***4.3.5 Statistical analysis***

Five participants with ADHD were excluded from the ERP analysis of the Go and NoGo condition and two participants with ADHD were excluded from the ERP analysis of the Cue condition due to having fewer than 20 artefact-free segments available for analysis. Four preterm-born participants were excluded from the ERP analysis of the NoGo and Cue condition and twelve preterm-born participants were excluded from the ERP analysis of the Go condition due to having fewer than 20 artefact-free segments available for analysis. Two control participants were excluded from the ERP analysis of the NoGo condition and

three control participants were excluded from the ERP analysis of the Go condition due to having fewer than 20 artefact-free segments available for analysis.

Data were analysed using random intercept models in Stata, to control for non-independence of the data, i.e. data coming from siblings of one family, using a 'robust cluster' command to estimate standard errors (Tye et al., 2012; Wood et al., 2009). This command was not available for correlational analyses, which were conducted to investigate the effect of age on ERP measures in the full sample. For these analyses siblings were removed from the ADHD (n=6), preterm (n=25) and control group (n=69) of the full sample. Post-hoc t-tests were conducted using the 'cltest' command (Herrin, 2012) to control for the non-independence of the data. Bonferroni correction was implemented to correct for multiple testing with a Bonferroni adjusted p-value=0.01. Effect sizes (Cohen's d), which were calculated using the difference in the means divided by the pooled standard deviation (Cohen, 1988), are also reported. According to Cohen (1988),  $d=0.20$  constitutes a small effect,  $d=0.50$  a medium effect and  $d=0.80$  a large effect.

As groups differed with regard to age in the full sample, age was included as a covariate in the analysis in the full sample. Groups in the full sample further differed in terms of IQ. Therefore, all analyses in the full sample were subsequently re-ran with IQ as a covariate, but results and significant levels did not change. In the age-matched subsample age was not included as a covariate since all three groups were matched on age. Although the groups in both the full sample and the age-matched subsample differed significantly on gender, gender was not included as a covariate in the group analyses to avoid controlling for ADHD status (Cheung et al., 2015a).

## 4.4 Results

### 4.4.1 Full sample

#### 4.4.1.1 Cognitive-performance measures

A trend-level significant effect of group emerged for RTV ( $t=2.73$ ,  $df=254$ ,  $p=0.007$ ). Post-hoc analyses revealed no significant difference between the ADHD and preterm groups ( $t=1.94$ ,  $df=160$ ,  $p=0.055$ ). However, the ADHD ( $t=-7.09$ ,  $df=160$ ,  $p<0.001$ ) and preterm groups ( $t=-5.83$ ,  $df=184$ ,  $p<0.001$ ) showed significantly increased RTV compared to the control group, with large effect sizes ( $d=1.07$  and  $d=0.79$  respectively) (Table 4.2). Groups did not differ on MRT ( $t=1.57$ ,  $df=254$ ,  $p=0.119$ ).

A significant effect of group emerged for the number of total omission errors ( $t=2.54$ ,  $df=254$ ,  $p=0.012$ ). Post-hoc analyses revealed no significant difference between the ADHD and preterm groups with regard to total omission errors ( $t=1.14$ ,  $d=160$ ,  $p=0.257$ ). However, the ADHD ( $t=-4.65$ ,  $d=160$ ,  $p<0.001$ ) and preterm groups ( $t=-2.19$ ,  $d=184$ ,  $p=0.030$ ) made significantly more omission errors than the control group, with moderate-to-large ( $d=0.69$ ) and small-to-moderate ( $d=0.30$ ) effect sizes respectively (Table 4.2). No significant effect of group emerged for the number of total commission errors ( $t=-0.27$ ,  $df=254$ ,  $p=0.787$ ).

#### 4.4.1.2 ERP results

##### 4.4.1.2.1 Cue condition

No significant main effect of group emerged for Cue-P3 amplitude ( $z=-1.66$ ,  $p=0.096$ ). The random intercept model yielded a significant main effect of group for CNV amplitude ( $z=4.62$ ,  $p<0.001$ ). Post-hoc tests revealed that the preterm group in the full sample demonstrated significantly attenuated CNV amplitude compared to the control group ( $t=-4.25$ ,  $df=203$ ,  $p<0.001$ ), with moderate effect size ( $d=0.51$ ) (Table 4.2), but not compared to the ADHD group ( $t=0.25$ ,  $df=177$ ,  $p=0.804$ ). The ADHD group showed significantly attenuated CNV amplitude compared to the control group ( $t=-4.24$ ,  $df=158$ ,  $p<0.001$ ), with a moderate-to-large effect size ( $d=0.61$ ) (Table 4.2).

#### 4.4.1.2.2 Go condition

No significant main effect of group emerged for Go-P3 amplitude ( $z=-2.28$ ,  $p=0.02$ ).

#### 4.4.1.2.3 NoGo condition

The random intercept model yielded no significant main effect of group for NoGo-N2 amplitude ( $z=-1.50$ ,  $p=0.133$ ). For NoGo-P3 amplitude, no significant main effect of group ( $z=-2.34$ ,  $p=0.015$ ) or recording site (FCz and Cz) ( $z=0.45$ ,  $p=0.652$ ) emerged. However, a significant group-by-recording site interaction emerged for NoGo-P3 amplitude ( $z=5.70$ ,  $p<0.001$ ). Post-hoc tests revealed that the preterm group showed significantly increased NoGo-P3 amplitude compared to the ADHD group at FCz ( $t=-2.87$ ,  $df=162$ ,  $p=0.024$ ), with small-to-moderate effect size ( $d=0.45$ ) (Table 4.2), but not at Cz ( $t=-0.30$ ,  $df=199$ ,  $p=0.769$ ). In addition, the preterm group demonstrated significantly reduced NoGo-P3 amplitude compared to the control group at Cz ( $t=4.08$ ,  $df=200$ ,  $p<0.001$ ), with moderate effect size ( $d=0.55$ ) (Table 4.2), but the two groups did not differ significantly at FCz ( $t=-1.14$ ,  $df=160$ ,  $p=0.255$ ). The ADHD group demonstrated significantly reduced NoGo-P3 amplitude compared to the control group at Cz ( $t=3.90$ ,  $df=155$ ,  $p<0.001$ ), with moderate-to-large effect size ( $d=0.68$ ) (Table 4.2), but not at FCz ( $t=1.33$ ,  $df=90$ ,  $p=0.187$ ).



**Table 4.2. Cognitive and ERP measures from the CPT-OX:** means (SDs) and effect sizes (Cohen's d) for the ADHD, preterm and control groups.

<i>Full sample</i>	Site	ADHD (n=75)	Preterm (n=145)	Control (n=153)	ADHD vs. Preterm effect size (d)	ADHD vs. Control effect size (d)	Preterm vs. Control effect size (d)
MRT	-	417.23 (69.0)	400.93 (72.2)	386.84 (48.1)	0.23	0.55	0.24
RTV	-	111.52 (58.3)	95.95 (49.6)	59.69 (43.8)	0.29	<b>1.07*</b>	<b>0.79*</b>
OE	-	2.48 (3.9)	1.69 (4.4)	0.77 (1.5)	0.19	0.69	0.30
CE	-	1.70 (2.3)	1.33 (2.8)	0.91 (1.4)	0.14	0.46	0.20
Cue-P3	Pz	5.24	6.91	6.35	0.47	0.43	0.18
CNV	Cz	-2.71	-2.81	-3.81	0.05	0.61*	0.51*
Go-P3	Pz	8.59	8.72	9.64	0.03	0.27	0.21
NoGo-P3	FCz	6.26	8.36	7.55	0.45*	0.29	0.17
	Cz	6.35	6.84	9.06	0.12	0.68*	0.55*
NoGo-N2	Fz	-5.45	-5.66	-5.67	0.06	0.07	0.03
<i>Age-matched subsample</i>	Site	ADHD (n=36)	Preterm (n=94)	Control (n=63)	ADHD vs. Preterm effect size (d)	ADHD vs. Control effect size (d)	Preterm vs. Control effect size (d)
MRT	-	412.50 (51.5)	391.44 (70.7)	386.44 (43.9)	0.32	0.56	0.08
RTV	-	110.53 (54.3)	86.51 (47.2)	84.40 (38.8)	0.48	0.58	0.05
OE	-	2.58 (4.2)	0.80 (1.5)	0.81 (1.9)	0.66	0.60	0.00
CE	-	1.50 (2.0)	0.84 (1.7)	0.98 (1.4)	0.36	0.31	0.09
Cue-P3	Pz	5.50 (3.7)	5.88 (3.0)	6.55 (2.5)	0.12	0.36	0.24
CNV	Cz	-3.29 (1.5)	-2.82 (2.0)	-3.77 (1.9)	0.25	0.28	0.49*
Go-P3	Pz	9.90 (3.6)	7.63 (5.0)	10.36 (3.8)	0.46*	0.12	0.57*
NoGo-P3	FCz	6.26 (4.1)	8.87 (5.9)	7.55 (5.3)	0.59*	0.29	0.28
	Cz	7.49 (4.9)	7.05 (5.3)	9.44 (4.1)	0.10	0.44*	0.59*
NoGo-N2	Fz	-5.44 (3.3)	-5.04 (3.6)	-4.78 (3.2)	0.11	0.24	0.11

Note: Large effect sizes in bold; \*p<0.05; ADHD=attention-deficit/hyperactivity disorder; MRT=mean reaction time in ms; RTV=reaction time variability in ms; OE=omission errors; CE=commission errors; CNV=contingent negative variation.

#### 4.4.1.3 Correlation results

Correlational analyses were conducted to investigate the effect of age on ERP measures. In the ADHD group, significant negative correlations emerged between age and Cue-P3 amplitude, as well as between age and Go-P3 amplitude (Table 4.3). A trend-level significant negative correlation emerged between age and NoGo-P3 amplitude at FCz. No significant correlations emerged between age and amplitude of the CNV, NoGo-P3 at Cz and NoGo-N2 (Table 4.3).

In the preterm group, significant correlations emerged between age and Cue-P3 amplitude, between age and Go-P3 amplitude as well as between age and NoGo-N2 amplitude (Table 4.3). No significant correlations emerged between age and amplitude of the CNV, NoGo-P3 at FCz and NoGo-P3 at Cz (Table 4.3).

In the control group, significant correlations emerged between age and Go-P3 amplitude as well as between age and NoGo-N2 amplitude (Table 4.3). A trend-level significant negative correlation emerged between age and NoGo-P3 amplitude at Cz. No significant correlations emerged between age and amplitude of the Cue-P3, CNV and NoGo-P3 at FCz (Table 4.3). These correlations suggest that age has at least some effect on certain ERP measures and highlight the importance of additional analyses on more closely age-matched groups.

**Table 4.3. Correlations between event-related potential (ERP) parameters and age across the ADHD, preterm and control groups of the full sample.**

<i>Full sample</i>	<i>Site</i>	<b>ADHD</b>	<b>Preterm</b>	<b>Control</b>
<b>Cue-P3</b>	Pz	-0.43**	-0.40**	-0.14
<b>CNV</b>	Cz	0.11	-0.03	0.15
<b>Go-P3</b>	Pz	-0.45**	-0.31**	-0.28*
<b>NoGo-P3</b>	FCz	-0.37	0.02	-0.16
	Cz	0.05	0.12	-0.25
<b>NoGo-N2</b>	Fz	-0.07	0.21*	0.42*

*Note:* \* $p < 0.05$ , \*\* $p < 0.01$ ; CNV=contingent negative variation.

## **4.4.2 Age-matched sample**

### *4.4.2.1 Cognitive-performance measures*

No significant effect of group emerged for RTV ( $t=-0.33$ ,  $df=155$ ,  $p=0.745$ ). Moreover, groups did not differ on MRT ( $t=-0.46$ ,  $d=155$ ,  $p=0.643$ ), number of total omission errors ( $t=-0.53$ ,  $df=155$ ,  $p=0.595$ ) or number of total commission errors ( $t=-1.16$ ,  $df=155$ ,  $p=0.247$ ). The moderate-to-large effect sizes for MRT, RTV and omission error between the ADHD and control groups ( $d=0.56-0.60$ ), as well as between the ADHD and preterm groups ( $d=0.32-0.66$ ) (Table 4.2) indicate that the lack of significant group differences likely results from an issue with statistical power.

#### 4.4.2.1.1 Cue condition

No significant main effect of group emerged for Cue-P3 amplitude ( $z=-1.48$ ,  $p=0.138$ ). The random intercept model yielded a significant main effect of group for CNV amplitude ( $z=3.31$ ,  $p<0.001$ ) (Figure 4.1). Post-hoc tests revealed that the preterm group demonstrated significantly attenuated CNV amplitude compared to the control group ( $t=-2.90$ ,  $df=138$ ,  $p=0.004$ ), with moderate effect size ( $d=0.49$ ) (Table 4.2), but not compared to the ADHD group ( $t=-1.23$ ,  $df=115$ ,  $p=0.220$ ). The ADHD and control groups did not differ significantly with regard to CNV amplitude ( $t=-1.32$ ,  $df=87$ ,  $p=0.191$ ).

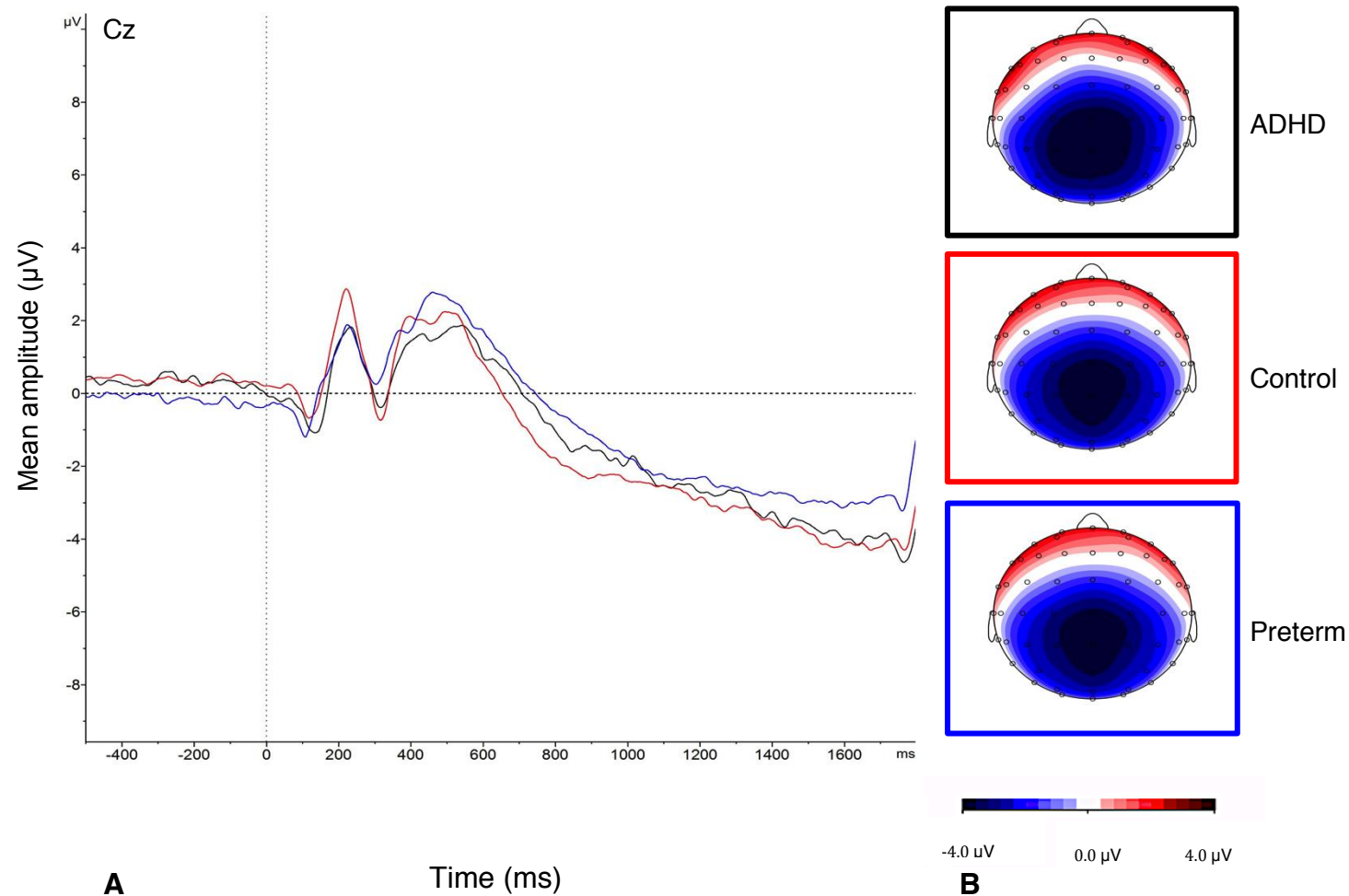
#### 4.4.2.1.2 Go condition

A significant main effect of group emerged for Go-P3 amplitude ( $z=-3.43$ ,  $p<0.001$ ) (Figure 4.2). Post-hoc tests revealed significantly reduced Go-P3 amplitude in the preterm group compared to the control ( $t=3.40$ ,  $df=144$ ,  $p<0.001$ ) and ADHD groups ( $t=2.18$ ,  $df=115$ ,  $p=0.03$ ), with moderate ( $d=0.57$ ,  $d=0.46$  respectively) effect sizes (Table 4.2). The ADHD and control groups did not differ with regard to Go-P3 amplitude ( $t=0.56$ ,  $df=89$ ,  $p=0.575$ ).

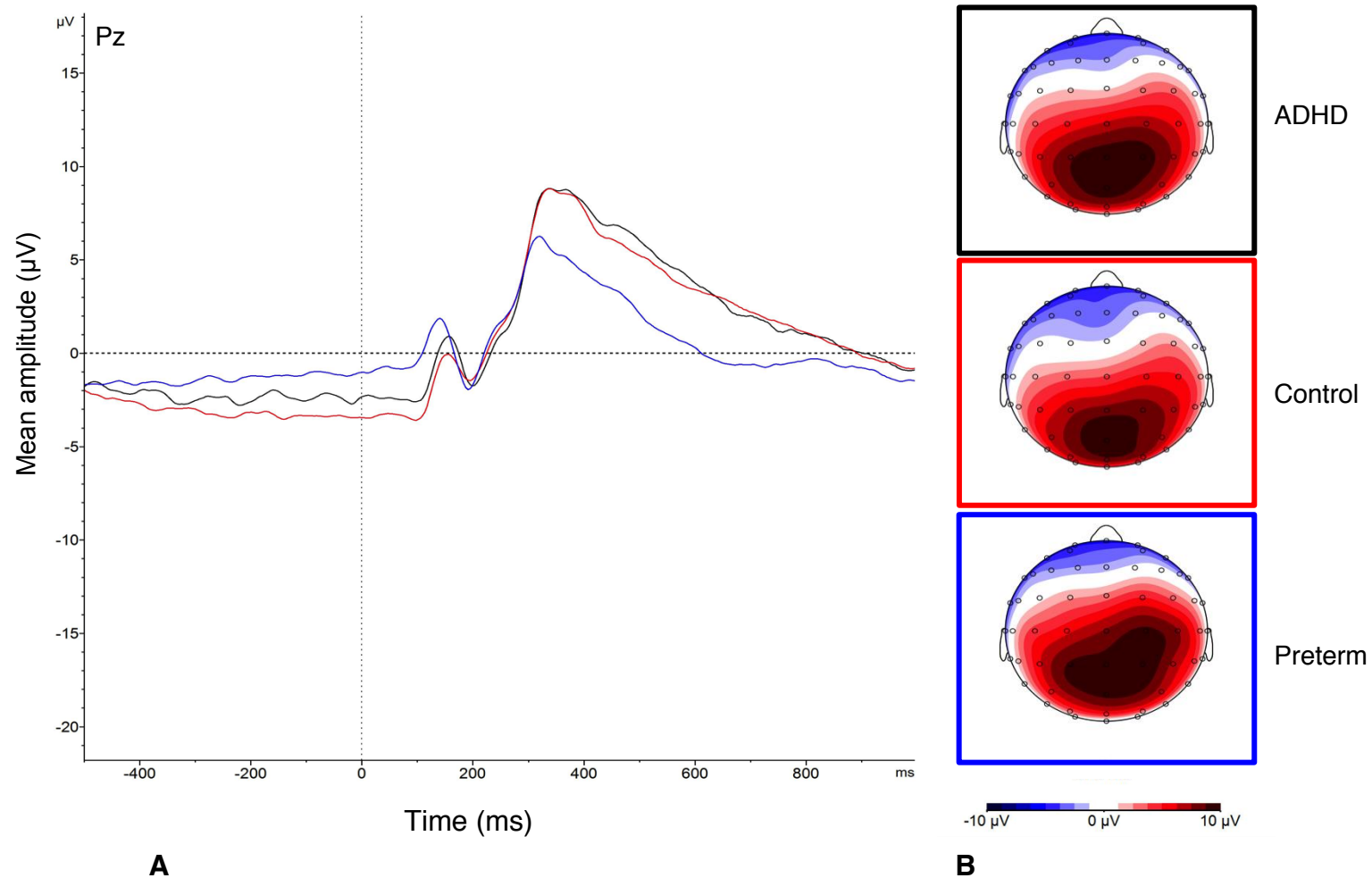
#### 4.4.2.1.3 NoGo condition

No significant main effect of group emerged for NoGo-N2 amplitude ( $z=-0.50$ ,  $p=0.617$ ). No significant main effect of group ( $z=-0.76$ ,  $p=0.447$ ) or recording site (FCz and Cz) ( $z=0.10$ ,  $p=0.924$ ) emerged for NoGo-P3 amplitude.

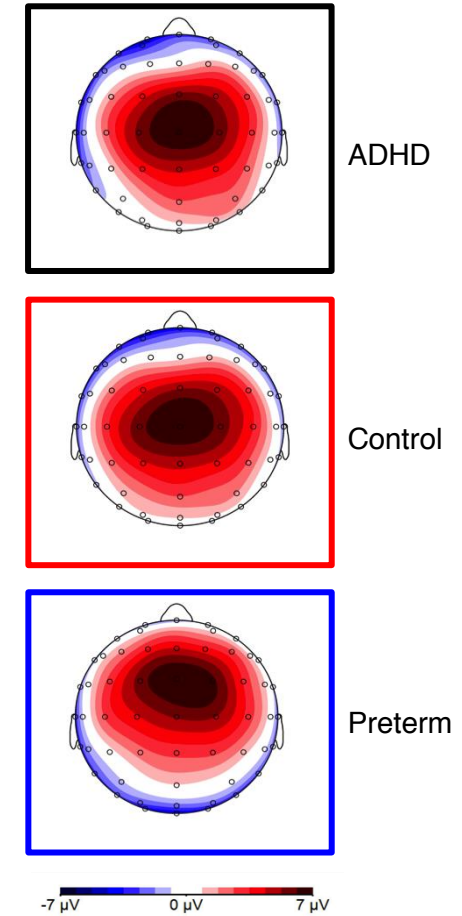
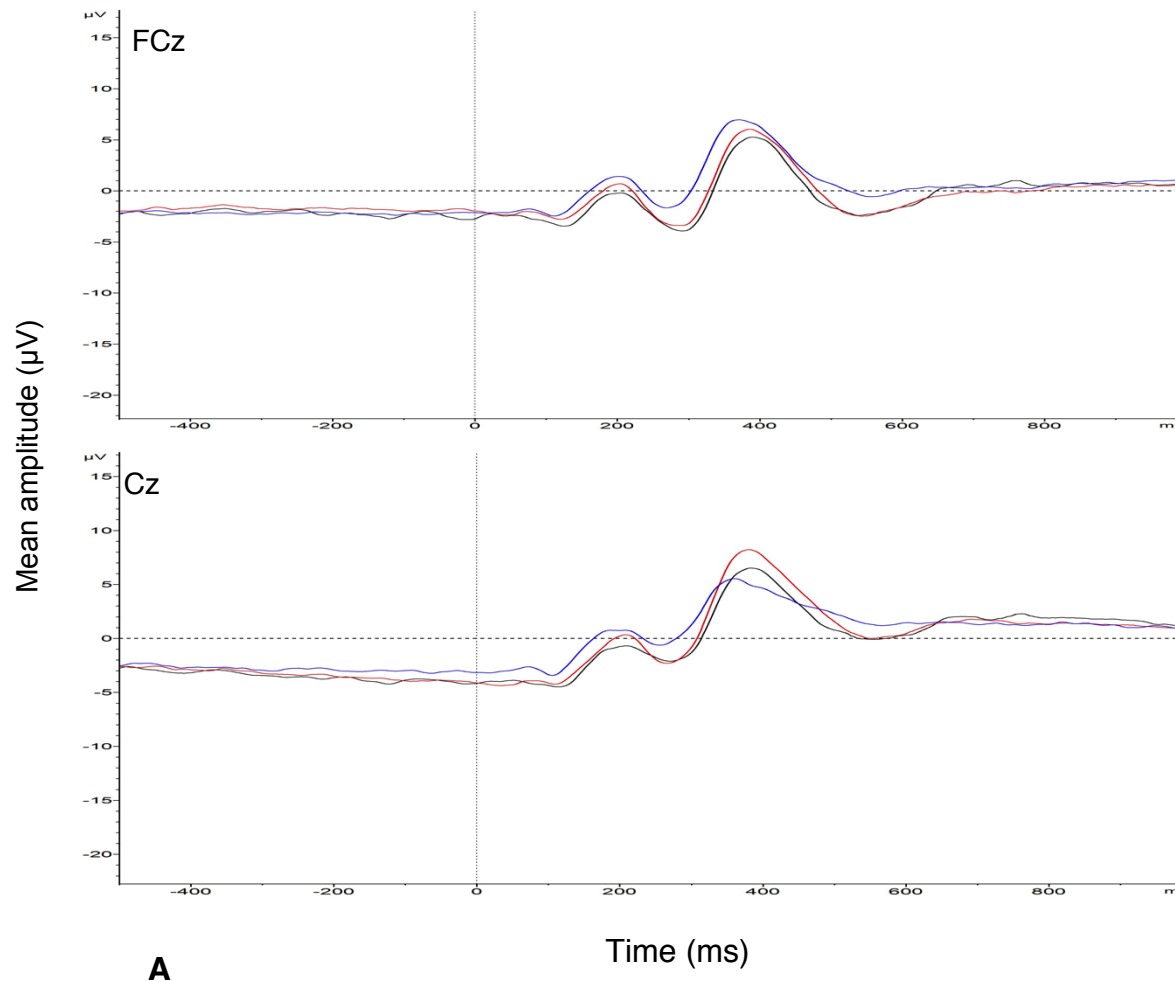
However, a significant group-by-recording site interaction emerged for NoGo-P3 amplitude ( $z=5.80$ ,  $p<0.001$ ) (Figure 4.3). Post-hoc tests revealed that the preterm group showed significantly increased NoGo-P3 amplitude compared to the ADHD group at FCz ( $t=-2.85$ ,  $df=107$ ,  $p=0.005$ ), with moderate effect size ( $d=0.59$ ) (Table 4.2), but not at Cz ( $t=0.30$ ,  $df=108$ ,  $p=0.763$ ). In addition, the preterm group demonstrated significantly reduced NoGo-P3 amplitude compared to the control group at Cz ( $t=3.53$ ,  $df=147$ ,  $p<0.001$ ), with moderate effect size ( $d=0.59$ ), but the two groups did not differ significantly at FCz ( $t=-1.74$ ,  $df=130$ ,  $p=0.084$ ). The ADHD group demonstrated significantly reduced NoGo-P3 amplitude compared to the control group at Cz ( $t=2.34$ ,  $df=130$ ,  $p=0.001$ ), with moderate effect size ( $d=0.44$ ), but not at FCz ( $t=1.33$ ,  $df=90$ ,  $p=0.187$ ).



**Figure 4.1. (A) Grand average event-related potentials (ERPs) to Cue stimuli** at the Cz electrode in the age-matched subsample, showing the CNV in the 1300-1650 ms window (ADHD, attention-deficit/hyperactivity disorder shown in black; the preterm group shown in blue; and the control group shown in red), and **(B) topographic maps for each group.**



**Figure 4.2. (A) Grand average event-related potentials (ERPs) to Go stimuli at the Pz electrode in the age-matched subsample, showing the Go-P3 in the 250-500 ms window (ADHD, attention-deficit/hyperactivity disorder shown in black; the preterm group shown in blue; and the control group shown in red), and (B) topographic maps for each group.**



**Figure 4.3. (A) Grand average event-related potentials (ERPs) to NoGo stimuli** at the FCz (above) and Cz (below) electrodes in the age-matched subsample, showing the NoGo-P3 in the 250-500 ms window (ADHD, attention-deficit/hyperactivity disorder shown in black; the preterm group shown in blue; and the control group shown in red), and **(B) topographic maps for each group.**

## 4.5 Discussion

Here, we directly compared term-born adolescents with ADHD, adolescents born preterm and term-born control adolescents on cognitive-performance and ERP measures from the CPT-OX. Since we demonstrated differences between the full sample and the age-matched subsample, as well as an effect of age on certain ERP components, the following discussion of results is based on the age-matched subsample. We provide evidence for response preparation (CNV), response execution (Go-P3) and response inhibition (NoGo-P3) impairments in individuals born preterm. While the observed response execution (Go-P3) impairments represent preterm birth-specific deficits, response inhibition (NoGo-P3) impairments were also observed in individuals with ADHD. With regard to response preparation (CNV), the ADHD group appears to lie intermediate between the preterm and control groups. The current study constitutes the first cognitive-neurophysiological comparison of attentional and inhibitory processing in term-born adolescents with ADHD and adolescents born preterm using the CPT-OX, and furthers our understanding of response preparation, execution and inhibition impairments in adolescents born preterm.

Our ERP results show a significant group difference in the amplitude of the P3 in response to Go stimuli, which was reduced in preterm-born adolescents compared to the other two groups. The Go-P3 has been linked to several attentional functions, such as evaluation of stimuli and resource allocation (Kok, 2000; Polich & Kok, 1995), and may reflect aspects of executive response control (Albrecht et al., 2013). Our results indicate, therefore, that adolescents born preterm show impaired response execution compared to adolescents with ADHD and control adolescents. Although an association between preterm birth and lower mean IQ scores has consistently been reported (Kerr-Wilson et al., 2012), our finding of a preterm birth-specific deficit is unlikely due to lower general cognitive ability since the preterm group of this study did not differ significantly from the control group on IQ scores and including IQ as a covariate had no effect on the results. However, since this is the first investigation of its kind, the findings of reduced Go-P3 amplitude in preterm-born adolescents require replication. In line with previous research, we found no Go-P3 differences between the ADHD and control groups (Albrecht et al., 2013;



Banaschewski et al., 2003; McLoughlin et al., 2010; van Leeuwen et al., 1998), although Go-P3 reductions have been reported in a small number of ADHD studies (Strandburg et al. 1996; Overtom et al. 1998; Banaschewski et al. 2004; Lawrence et al. 2005).

Response inhibition impairments, as indexed by abnormal NoGo-P3 amplitude, were observed in both preterm-born adolescents and adolescents with ADHD. A study investigating ADHD case-control differences on data partially overlapping with the current analysis previously reported attenuated amplitude of the NoGo-P3, as well as reduced CNV and Cue-P3 amplitude in adolescents with ADHD compared to control adolescents (Cheung et al., 2015a). The significant group-by-recording site interactions in the current study, supported by topographic maps of NoGo-P3 mean amplitude, indicate a degree of group-specificity in relation to the response inhibition impairments. While both the ADHD and preterm groups demonstrated significantly reduced NoGo-P3 amplitude compared to controls at the vertex, the preterm group showed a more frontally distributed NoGo-P3 component compared to adolescents with ADHD and controls, which was significantly increased compared to the ADHD group. These findings extend previous cognitive research, which has indicated deficits in response inhibition in individuals born preterm (Burnett et al., 2015; Mulder et al., 2009; Nosarti et al., 2007; Stålnacke et al., 2014; Taylor et al., 2004). The reduced P3 amplitude in response to NoGo stimuli in the ADHD group compared to controls replicates a pattern of impaired response inhibition that is well established in the ADHD literature (Albrecht et al., 2013; Doehnert et al., 2013; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011). Although ADHD symptom scores were increased in the preterm group compared to controls (as previously reported in chapter 3), further analyses will need to elucidate how the ADHD symptoms in the preterm group are related to performance on cognitive-neurophysiological measures such as the NoGo-P3, which presents shared impairments between the ADHD and preterm groups. Future research should also examine whether the performance of preterm-born individuals on the cognitive-neurophysiological measures investigated here is related to other psychiatric symptoms.

We further identified CNV abnormalities in the preterm group compared to the control group, suggestive of impaired attentional orienting and response preparation (van Leeuwen et al., 1998). The attenuated CNV amplitude in adolescents born preterm is in accordance with previous evidence of abnormalities in attentional orienting as indexed by a reduced P3a component during a distraction paradigm in children born preterm (Mikkola et al., 2010). The ADHD group demonstrated response preparation that was intermediate between that of the preterm and control groups. Previous studies have reported reduced CNV in children, adolescents and adults with ADHD (Albrecht et al., 2013; Doehnert et al., 2013; McLoughlin, Asherson, et al., 2011). The lack of significant CNV abnormalities in the ADHD group is, therefore, inconsistent with previous work. However, not all studies have reported ADHD case-control differences in CNV amplitude (Tye, Asherson, et al., 2014; van Leeuwen et al., 1998), possibly due to developmental changes in the amplitudes (Jonkman, Lansbergen, & Stauder, 2003; Jonkman, 2006; Segalowitz & Davies, 2004) and topographies of the CNV (Klein & Feige, 2005). The non-significant finding with regard to CNV in the ADHD group may, therefore, be due to developmental changes. This idea is supported by analyses of the full sample, which revealed reduced CNV amplitude with moderate effect size compared to the control group.

The lack of a difference between the three groups with regard to NoGo-N2 amplitude is inconsistent with previous research demonstrating abnormalities in NoGo-N2 amplitude in children born very preterm (<32 weeks) using an auditory oddball paradigm (Hövel et al., 2014; Mikkola et al., 2007), as well as in individuals with ADHD using flanker tasks (Albrecht et al., 2008; Johnstone et al., 2009; McLoughlin et al., 2009). However, the CPT-OX is a task with low conflict-monitoring demands and previous studies using the CPT-OX have also not been able to demonstrate an attenuated NoGo-N2 in individuals with ADHD (Albrecht et al. 2013; Doehnert et al. 2013; McLoughlin et al. 2010). Similarly, we found no difference in Cue-P3 amplitude between adolescents with ADHD and control adolescents. While these findings do not replicate some previous investigations showing a reduced Cue-P3 in children, adolescents and adults with ADHD (Albrecht et al., 2013; Doehnert et al., 2010; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011; Tye, Asherson, et al., 2014), they are

in line with other studies reporting no case-control difference in Cue-P3 in adults with ADHD (Dhar et al., 2010; Michelini et al., 2015). Age effects may play a role in the discrepancy between studies since developmental changes have been reported for the Cue-P3, suggesting that ADHD-control differences may decline with age (Doehnert *et al.* 2013). Further studies should investigate the differences between ADHD and preterm birth in tasks with higher conflict-monitoring demands as well as in longitudinal studies to clarify potential age-effects.

While ERP measures of response inhibition and response execution differentiated the ADHD, preterm and control groups, cognitive-performance data did not suggest differences between the groups. Yet, the effect sizes between the ADHD and control groups, as well as between the ADHD and preterm groups, indicate that the lack of significant group differences likely results from a lack of statistical power to detect these differences. According to effect sizes, MRT, RTV and omission errors are increased in ADHD compared to both the preterm and control groups, consistent with previous research reporting lower accuracy and higher MRT and RTV in ADHD (Kuntsi & Klein, 2012; Kuntsi et al., 2010). Differences between the ADHD and preterm groups observed at the neurophysiological but not at the cognitive-performance level may indicate greater specificity of the neurophysiological markers in detecting differences between these groups.

Here, results were presented and interpreted without baseline correction since most previous ERP analyses on CPT-OX did not apply a baseline correction (Albrecht et al., 2013; Banaschewski et al., 2004; Doehnert et al., 2013; McLoughlin et al., 2010; McLoughlin, Asherson, et al., 2011), including the study partially overlapping with the current analysis (Cheung et al., 2015a). Additional analyses with baseline corrections were run in the age-matched sample to enable comparison to analyses where such corrections were applied. Baseline corrections did not affect the results with regard to group differences, except for group differences on the CNV, which became non-significant. Since the baseline correction process subtracts the mean prestimulus voltage from the ERP waveform, it is not surprising that group differences on the CNV, a

prestimulus ERP component that represents response preparation, became non-significant.

Certain limitations should be taken into consideration. Our sample of individuals born preterm may not generalise to clinical samples or samples established through support groups, as it was drawn from the general population. Yet, a general population sample reduces the risk of referral and selection biases associated with clinical samples. In addition, as reflected in its above average IQ, the control sample may also not be fully representative of other typically developing adolescents. Furthermore, we were unable to examine component latency due to adopting a mean amplitude measure. A mean amplitude measure has the advantage of being more robust than a peak amplitude measure with regard to the high intra-individual variability across trials common in ADHD, which may reduce the amplitude of ERP components (McLoughlin, Makeig, et al., 2014).

In conclusion, this study provides evidence for impairments in brain processes involved in response preparation, response execution and response inhibition in adolescents born preterm. While some of the impairments found in adolescents born preterm overlap with those found in term-born adolescents with ADHD, the preterm group also shows unique deficits, indicating more wide-ranging deficits in the preterm group compared to the ADHD group. This idea is supported by research suggesting that, as well as being a risk factor for ADHD, preterm birth presents a risk factor for other psychiatric disorders, such as schizophrenia, bipolar disorder and autism spectrum disorder (D'Onofrio et al., 2013; Samantha Johnson & Marlow, 2014; Moster et al., 2008; Treyvaud et al., 2013). The late third trimester (32–40 weeks' gestation) serves as a critical period to lay the foundation of vital brain networks (Ball et al., 2014; van den Heuvel et al., 2014). It is, therefore, conceivable that preterm birth may result in trauma to the brain networks associated with ADHD, as well as networks associated with additional impairments. These results, as well as the findings that ADHD symptom scores are increased in the preterm group compared to controls, suggest that preterm birth may present a risk factor for both ADHD and additional impairments. As this is one of the first studies of this kind, these findings require replication in larger-scale studies.

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## **Chapter 5. A longitudinal twin study of the direction of effects between ADHD symptoms and IQ**

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RESEARCH ARTICLE

# A Longitudinal Twin Study of the Direction of Effects between ADHD Symptoms and IQ

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## Abstract

While the negative association between ADHD symptoms and IQ is well documented, our knowledge about the direction and aetiology of this association is limited. Here, we examine the association of ADHD symptoms with verbal and performance IQ longitudinally in a population-based sample of twins. In a population-based sample of 4,771 twin pairs, DSM-IV ADHD symptoms were obtained from the Conners' Parent Rating Scale-Revised. Verbal (vocabulary) and performance (Raven's Progressive Matrices) IQ were assessed online. ADHD symptom ratings and IQ scores were obtained at ages 12, 14 and 16 years. Making use of the genetic sensitivity and time-ordered nature of our data, we use a cross-lagged model to examine the direction of effects, while modelling the aetiologies of the association between ADHD symptoms with vocabulary and Raven's scores over time. Although time-specific aetiological influences emerged for each trait at ages 14 and 16 years, the aetiological factors involved in the association between ADHD symptoms and IQ were stable over time. ADHD symptoms and IQ scores significantly predicted each other over time. ADHD symptoms at age 12 years were a significantly stronger predictor of vocabulary and Raven's scores at age 14 years than vice versa, whereas no differential predictive effects emerged from age 14 to 16 years. The results suggest that ADHD symptoms may put adolescents at risk for decreased IQ scores. Persistent genetic influences seem to underlie the association of ADHD symptoms and IQ over time. Early intervention is likely to be key to reducing ADHD symptoms and the associated risk for lower IQ.

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is associated with lower mean IQ scores. The correlation between IQ and ADHD symptoms reported in general population samples ranges from  $-0.2$  to  $-0.4$  [1,2]. A meta-analysis of 123 studies estimated a 7–11-point difference in full-scale IQ between control individuals and individuals diagnosed with ADHD [3]. Although

**Competing Interests:** The authors have declared that no competing interests exist.

not significantly different, the effect size (ES) of verbal IQ (VIQ; ES = 0.67; 95% CI 0.58–0.76) was larger than that of performance IQ (PIQ; ES = 0.58; 95% CI 0.48–0.68). A large family-based study of 238 ADHD families (545 children) and 147 control families (271 children) also found that children diagnosed with ADHD and their affected and unaffected siblings had lower mean scores on VIQ, but not PIQ [4]. Moreover, lower VIQ than PIQ has been reported for adolescents diagnosed with ADHD [5].

In a clinical sample, children with IQs < 70 showed more severe ADHD symptoms than children with IQ > 70 [6]. Lower IQ is also associated with higher levels of externalising and behavioural problems in individuals with ADHD [7]. IQ has been shown to positively impact the response to pharmaceutical treatment in ADHD [8–11]. Therefore, IQ impacts on overall outcome in individuals with ADHD and is a good predictor of life success in the general population [12,13].

The heritability of ADHD symptoms is high at ~70% [14]. The extent of genetic factors influencing ADHD symptoms are relatively stable, although new as well as stable genetic influences are seen at different developmental stages [15–17]. For IQ, a developmental pattern is observed, whereby the extent of genetic influences on IQ gradually increases with age: heritability is estimated at around 30–60% in middle childhood and increases to 50–80% in adolescence and adulthood [18–20]. The largely genetic origin of the association of IQ and ADHD symptoms was initially shown in a large population-based sample of 5-year old twins, where 86% of the phenotypic correlation between ADHD symptom and IQ scores and 100% of the association between ADHD research diagnosis and IQ scores could be accounted for by genetic factors [1]. The genetic correlations, which indicate the degree to which genetic influences contributing to one trait are shared with genetic influences contributing to another trait, were  $r_A = -0.45$  between IQ and ADHD symptoms and  $r_A = -0.59$  between IQ and ADHD research diagnosis [1]. Significant genetic correlations have since been found in population-based twin samples of similar age [21,22], and in twin samples aged 7 to 10 years [2,23].

Although the shared genetic origins of and negative correlation between ADHD and IQ are well documented, little is known about the direction of effects or the genetic overlap between these variables at different developmental stages. The first objective of this study was to establish the developmental pattern of the association of ADHD symptoms with VIQ and PIQ in a population-based twin sample. While ADHD symptoms diminish in severity over the course of puberty (~ages 12–16 years [24]), individuals with high levels of ADHD symptoms are at increased risk of continuing problems related to ADHD during adolescence [25,26]. We are therefore, interested in the developmental pattern of the association of ADHD symptoms with VIQ and PIQ at ages 12, 14 and 16 years; a period of rapid developmental change for which both ADHD and IQ data were available in our large twin sample.

Previous research suggests a greater negative association between ADHD symptoms and VIQ than between ADHD symptoms and PIQ [3–5]. VIQ and PIQ are, thus, examined separately, allowing us to explore potential strengths and weaknesses associated with ADHD symptoms. The second aim was to examine the genetic and environmental aetiologies of the association of ADHD symptoms with VIQ and PIQ within time point, and their stability across time. Making use of the inherently time-ordered nature and genetic sensitivity of the data, we use a cross-lagged model to address these two objectives: namely, we establish the direction of effects, while modelling the genetic and environmental variance and covariance structure of the data separately for VIQ and PIQ.

## Methods

### Sample

Data came from the Twins Early Development Study (TEDS), a UK population-representative sample of twins born in England and Wales between 1994 and 1996 [27]. Zygosity of the twins was initially based on physical similarity ratings and later verified using genotyping. Participants were excluded following pre- or perinatal complications or if one or both twins suffered from any severe medical condition (e.g. autism spectrum disorder, cerebral palsy, Down's syndrome). Uncertain sex or zygosity and failure to provide information at recruitment were also exclusion criteria. After exclusion, 1,745 monozygotic (MZ) and 3,026 dizygotic (DZ) twin pairs were included in the model-fitting analysis. 46.1% of the participants were male. All twins (born in 1994, 1995 or 1996) were contacted simultaneously in order to simplify administration. Thus, twin ages ranged from 10.1 to 13.7 years of age at time point 1 ( $t_1$ ; mean age = 11.6 years,  $SD = 0.68$ ), from 12.8 to 15.8 years of age at time point 2 ( $t_2$ ; mean age = 14.0 years,  $SD = 0.60$ ) and from 15.8 to 17.3 years of age at time point 3 ( $t_3$ ; mean age = 16.5 years,  $SD = 0.27$ ).

### Ethics Statement

Ethical approval was obtained from the King's College London, Institute of Psychiatry, Psychology and Neuroscience ethics committee and all participants and/or their parents gave written consent for participation in this study.

### Measures

**ADHD symptoms.** ADHD symptoms were measured using the DSM-IV items on the Conners' Parent Rating Scale-Revised [28]. The scores on the nine-item hyperactive-impulsive symptoms subscale were added to the scores on the nine-item inattentive symptoms subscale to form a total DSM-IV ADHD symptoms subscale. At  $t_1$ , parent booklets enclosing the Conners' Parent Rating Scale-Revised were sent in the post. At  $t_2$  and  $t_3$ , similar parent booklets were sent to the families as online versions designed to mimic the paper version's appearance.

**General cognitive ability.** All IQ assessments were administered online. See Haworth et al. [29] for details on how these web-based tests were created. A web-based multiple-choice version of the WISC-III vocabulary subtest was used to measure VIQ at  $t_1$  and  $t_2$ . At  $t_3$ , an online version of the Mill Hill Vocabulary scale was used as an indicator of VIQ because the WISC is not designed to measure intelligence beyond age 16 years. In both the WISC-III vocabulary subtest and the Mill Hill Vocabulary scale, the participant's task was to select the correct synonym for a word from a list of alternatives provided. Here, we refer to the outcome of these measures as vocabulary scores. PIQ was measured using a web-based version of the Raven's Progressive Matrices test [30] at all three time points. At age 16 years, these web-based IQ tests were validated by comparing the online results for a subsample with their results on traditional paper-and-pencil tests. An average correlation of 0.72 between online and offline tests, administered 2 months apart, was found, providing support for the validity of these web-based tests [27].

Widespread access to internet connections in the UK has made online testing an attractive possibility for collecting data on large samples. Studies have shown that web-based findings are consistent with findings from traditional methods [31]. In our study, parents supervised the testing by coming online first using a family username and password, watching a demonstration and completing a consent form. The twins each had a unique ID number as well as a



family number and completed the test in turn. Parents were urged neither to assist the twins with answers nor to allow the twins to see each other's answers.

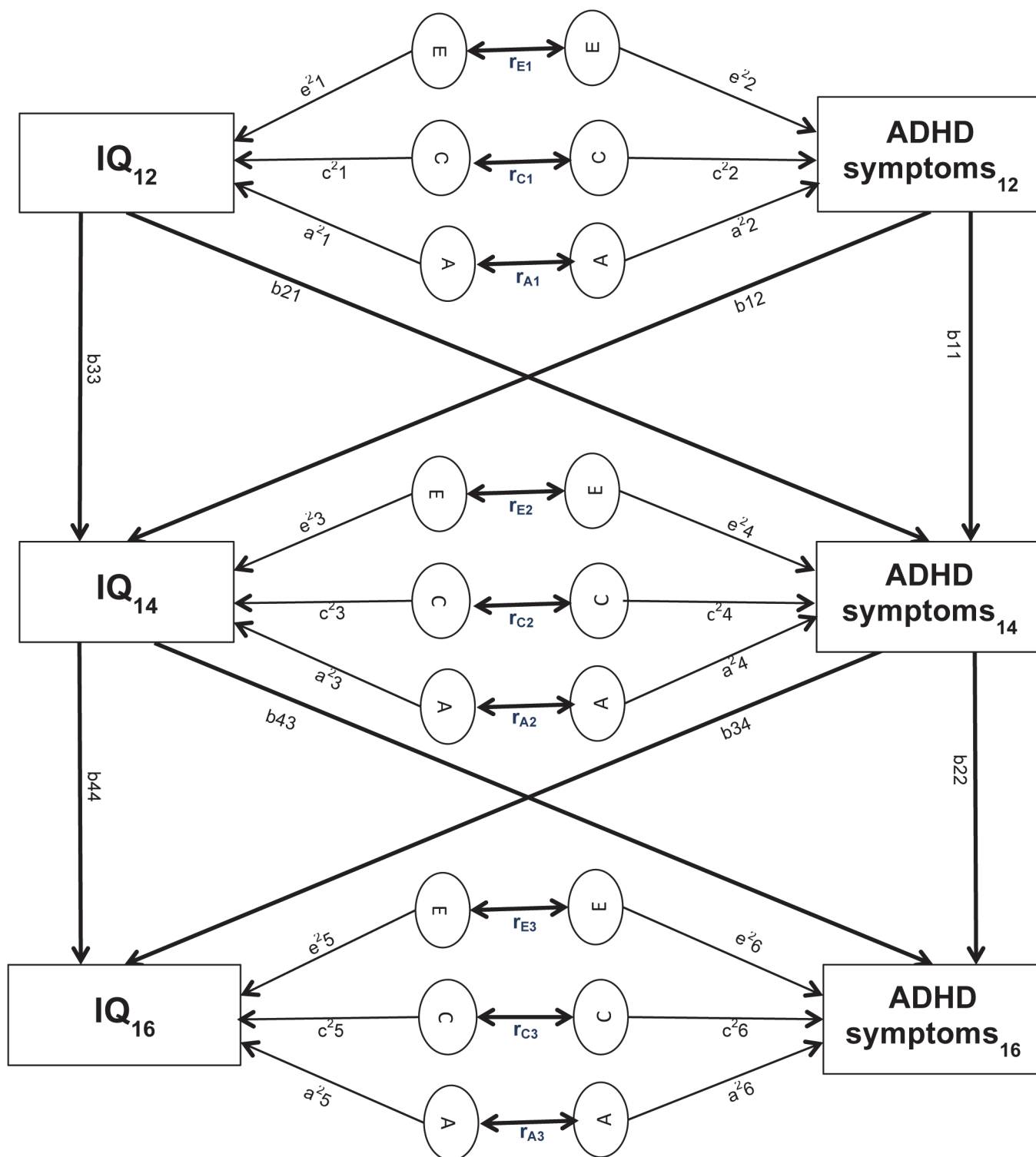
## Statistical analyses

All analyses were conducted in OpenMx [32]. This program deals with incomplete data (missing at random) by calculating the log likelihood of the data for each observation using raw maximum likelihood estimation. Standard regression-based corrections for age and sex were applied to raw scores [33] and residual scores were analysed. Means and variances within traits, as well as phenotypic correlations across traits, were equated across twins in a pair and zygosity group in order to generate phenotypic correlation coefficients representative of the entire sample while taking the non-independence of the data into account (i.e. data from related individuals). Separate analyses were conducted for vocabulary and Raven's scores.

**The cross-lagged twin model.** *Time-specific effects:* The applied model specifies the time-specific genetic and environmental components of (co)variance in a standard bivariate genetic model using biometrical genetics theory [34]. Estimation of the additive genetic effects (A), shared environment (C) and non-shared environment (E) for each trait is based on the fact that MZ and DZ twins have different degrees of correlation for the genetic component (1 vs 0.5), but the same degree of correlation for shared (1) and non-shared environmental factors (0). This is due to the expectation that MZ twins share 100% and DZ twins share on average 50% of their inherited DNA sequence; yet both MZ and DZ twins share many aspects of their environment by virtue of being born at the same time and place and growing up in the same family. The MZ:DZ correlation ratio indicates the relative importance of the A, C and E components for each trait. In the bivariate twin analysis, MZ and DZ correlations are compared across traits: i.e., one twin's ADHD symptoms are correlated with the co-twin's IQ score. If the cross-trait cross-twin correlations are greater for MZ than for DZ twins, this implies that genetic factors contribute to the phenotypic correlation between the two traits. Fig 1 depicts genetic (A), shared environmental (C) and non-shared environmental (E) influences on ADHD symptoms and IQ. Non-shared environmental influences also include measurement error. Fig 1 also presents genetic and environmental correlations ( $r_A$ ,  $r_C$ ;  $r_E$ ), which can range from -1 to 1, and represent the extent to which genetic and environmental influences on ADHD symptoms and the IQ subtests overlap (regardless of their individual heritabilities). Furthermore, phenotypic correlations can be attributed to genetic and environmental influences. The proportion of the phenotypic correlation between ADHD symptoms and the IQ subtests that is due to genetic influences at age 12 years, for example, can be derived by calculating  $[(a_1 \times r_{A1} \times a_2) / (\text{phenotypic correlation at age 12 years} \times 100)]$  (Fig 1).

*Cross-lagged effects:* The model specifies the across-time correlations by means of causal cross-lagged paths, which connect different measures across time points (Fig 1:  $b_{12}$ ,  $b_{21}$ ,  $b_{34}$ ,  $b_{43}$ ). The stability paths connect the same measure across time points (Fig 1:  $b_{11}$ ,  $b_{22}$ ,  $b_{33}$ ,  $b_{44}$ ). The stability and cross-lagged paths take the form of partial regression coefficients, which take into account the pre-existing association between ADHD symptoms and IQ, as well as controlling for stability or cross-lagged effects.

In order to establish the extent to which the same or different aetiological factors influence ADHD symptoms and IQ over time, genetic and environmental variances were divided into variance specific to  $t_2$  and  $t_3$ , and variance transmitted from  $t_1$  to  $t_2$ , and from  $t_2$  to  $t_3$ . Variance can be transmitted via the stability paths. The genetic variance transmitted via the stability path to ADHD symptoms from  $t_1$  to  $t_2$ , for example, is calculated as  $a_2^2 \times b_{11}^2$  (Fig 1). Variance can also be transmitted via the cross-lagged paths. The genetic variance transmitted to ADHD symptoms via the cross-lagged path from  $t_1$  to  $t_2$ , for example, is calculated as  $a_1^2 \times$



**Fig 1. Cross-lagged twin model.** Circles represent latent genetic (A), shared environmental (C) and non-shared environmental (E) factors for ADHD symptoms and IQ at time 1 (age 12), time 2 (age 14) and time 3 (age 16). Paths from the latent A, C, E factors to the observed variables ( $a_1$ – $a_6$ ,  $c_1$ – $c_6$ ,  $e_1$ – $e_6$ ) represent genetic and environmental contributions to ADHD symptoms and IQ scores. The environmental and genetic correlations between ADHD symptoms and IQ for each time point are indicated below the arrows connecting the respective circles ( $r_E$ ,  $r_C$ ,  $r_A$ ). Stability paths ( $b_{11}$ ,  $b_{22}$ ,  $b_{33}$ ,  $b_{44}$ ) connect the same traits across time. Cross-lagged paths ( $b_{12}$ ,  $b_{21}$ ,  $b_{34}$ ,  $b_{43}$ ) connect different traits across time.

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**Table 1. Phenotypic correlations between ADHD symptom and vocabulary scores.**

	ADHD sympt <sub>1</sub>	Vocabulary <sub>1</sub>	ADHD sympt <sub>2</sub>	Vocabulary <sub>2</sub>	ADHD sympt <sub>3</sub>	Vocabulary <sub>3</sub>
ADHD sympt <sub>1</sub>	1					
Vocabulary <sub>1</sub>	-.19 (-.20/-.16)	1				
ADHD sympt <sub>2</sub>	.77 (.77/.79)	-.19 (-.21/-.16)	1			
Vocabulary <sub>2</sub>	-.23 (-.27/-.21)	.48 (.45/.50)	-.23 (-.27/-.22)	1		
ADHD sympt <sub>3</sub>	.57 (.56/.58)	-.17 (-.19/-.15)	.74 (.73/.75)	-.24 (-.28/-.23)	1	
Vocabulary <sub>3</sub>	-.16 (-.20/-.14)	.20 (.19/.22)	-.18 (-.23/-.16)	.41 (.38/.44)	-.16 (-.21/-.14)	1

95% confidence intervals are provided in brackets.

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b21<sup>2</sup>. Furthermore, variance can be transmitted via the covariation of ADHD symptoms and IQ. The genetic variance transmitted to ADHD symptoms via the covariation of ADHD symptoms and IQ from t<sub>1</sub> to t<sub>2</sub>, for example, is calculated as 2x (b21 x a1 x r<sub>A1</sub> x a2 x b11). To examine the changes in genetic and environmental aetiologies of the association between ADHD symptoms and IQ, the covariance between ADHD symptoms and IQ was divided into covariance specific to t<sub>2</sub> or t<sub>3</sub> and covariance shared with the previous time point.

## Results

### Phenotypic correlations

The phenotypic across-trait correlations between ADHD symptoms and vocabulary scores ranged from -0.16 to -0.24 (Table 1). The phenotypic across-trait correlations between ADHD symptoms and Raven's scores ranged from -0.18 to -0.22 (Table 2). Phenotypic within-trait across-time correlations were high for ADHD symptoms (range: 0.57–0.77; Tables 1 and 2) and moderate for vocabulary (range: 0.20–0.48; Table 1) and Raven's scores (range: 0.35–0.63; Table 2).

### Genetic and environmental aetiologies

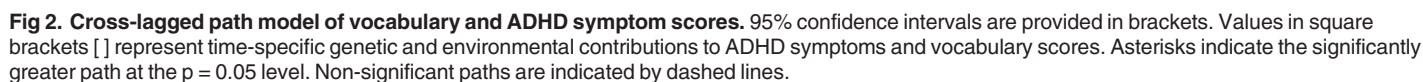
Heritabilities of ADHD symptoms were high at each of the three time points (range: 0.65–0.82; Figs 2 and 3). Heritabilities of vocabulary (range: 0.24–0.29; Fig 2) and Raven's scores (range 0.30–0.39; Fig 3) were moderate at all three time points. The genetic correlation between the total variance of ADHD symptoms and vocabulary scores was significant at each time point (r<sub>A1</sub> = -0.29, r<sub>A2</sub> = -0.31, r<sub>A3</sub> = -0.20; Fig 2). At t<sub>1</sub>, t<sub>2</sub> and t<sub>3</sub>, 74%, 61% and 50% of the phenotypic correlation between ADHD symptoms and vocabulary scores were attributable to genetic influences, respectively (Table 3). The genetic correlations between the total variance of ADHD

**Table 2. Phenotypic correlations between ADHD symptom and Raven's Standard Progressive Matrices scores.**

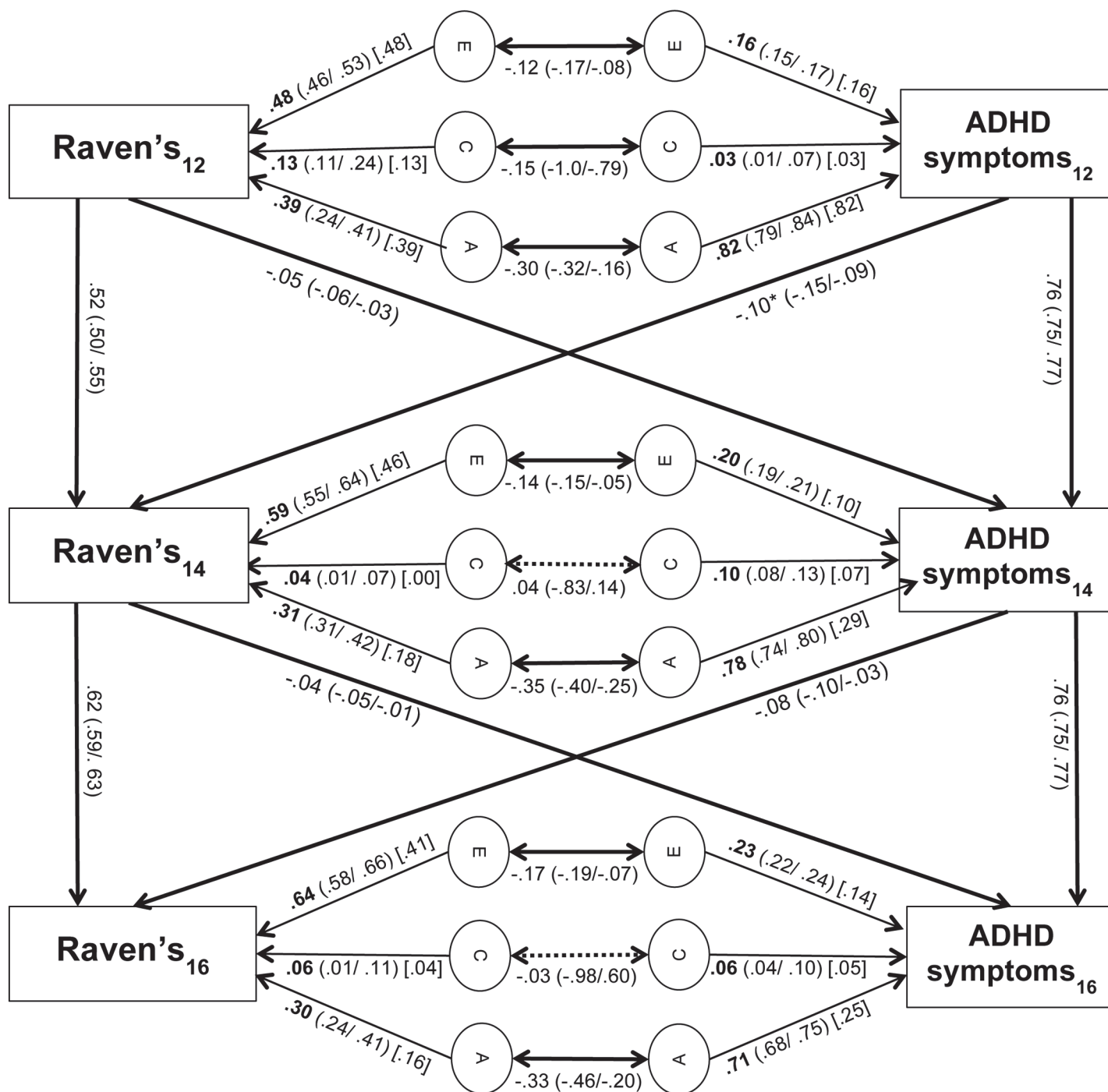
	ADHD sympt <sub>1</sub>	Raven's <sub>1</sub>	ADHD sympt <sub>2</sub>	Raven's <sub>2</sub>	ADHD sympt <sub>3</sub>	Raven's <sub>3</sub>
ADHD sympt <sub>1</sub>	1					
Raven's <sub>1</sub>	-.21 (-.24/-.17)	1				
ADHD sympt <sub>2</sub>	.76 (.75/.77)	-.21 (-.23/-.19)	1			
Raven's <sub>2</sub>	-.21 (-.24/-.18)	.54 (.47/.56)	-.22 (-.26/-.20)	1		
ADHD sympt <sub>3</sub>	.59 (.57/.60)	-.18 (-.19/-.13)	.77 (.76/.78)	-.20 (-.24/-.18)	1	
Raven's <sub>3</sub>	-.19 (-.20/-.15)	.35 (.29/.38)	-.22 (-.24/-.17)	.63 (.60/.65)	-.22 (-.24/-.18)	1

95% confidence intervals are provided in brackets.

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7 / 16



**Fig 3. Cross-lagged path model of Raven's and ADHD symptom scores.** 95% confidence intervals are provided in brackets. Values in square brackets [ ] represent time-specific genetic and environmental contributions to ADHD symptoms and Raven's Progressive Matrices Scores. Asterisks indicate the significantly greater path at the p = 0.05 level. Non-significant paths are indicated by dashed lines.

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symptoms and Raven's scores were also significant at all three time points ( $r_{A1} = -0.30$ ,  $r_{A2} = -0.35$ ,  $r_{A3} = -0.33$ , Fig 3). At  $t_1$ ,  $t_2$  and  $t_3$ , 81%, 77% and 68% of the phenotypic correlation between ADHD symptoms and Raven's scores were attributable to genetic influences, respectively (Table 4).

**Table 3. Proportions of the phenotypic correlations between ADHD symptoms and vocabulary scores due to genetic (A), shared environmental (C) and non-shared environmental (E) influences.**

$r_{ph}$	Time 1	Time 2		Time 3	
	-0.19	-0.23		-0.16	
% of $r_{ph}$ due to		Total <sup>a</sup>	Time-specific <sup>b</sup>	Total <sup>a</sup>	Time-specific <sup>b</sup>
<b>A</b>	74% (0.14)	61% (0.14)	30% (0.07)	50% (0.08)	25% (0.04)
<b>C</b>	16% (0.03)	17% (0.04)	9% (0.02)	12.5% (0.02)	12.5% (0.02)
<b>E</b>	10% (0.02)	22% (0.05)	13% (0.03)	37.5% (0.06)	25% (0.04)

ADHD = attention deficit hyperactivity disorder;  $r_{ph}$  = phenotypic correlation

<sup>a</sup>Proportions of the phenotypic correlation due to total genetic or environmental influences (i.e. transmitted plus age-specific effects).

<sup>b</sup>Proportions of the phenotypic correlation due to time-specific genetic or environmental influences specific to early adolescence.

Figures in parentheses refer to the absolute contributions of A, C and E respectively to the phenotypic correlations between ADHD symptoms and vocabulary scores.

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For ADHD symptoms, 38–39% of genetic variance (i.e. of the heritability shown in Figs 2 and 3), 33–70% of shared environmental variance, and 50–80% of non-shared environmental variance were due to time-specific aetiological influences at  $t_2$ . At  $t_3$ , 36–79% of genetic variance, 83–92% of shared environmental variance, and 61–84% of non-shared environmental variance were due to time-specific aetiological influences (Tables 5 and 6). For vocabulary scores, 68% of genetic variance, 67% of shared environmental variance and 81% of non-shared environmental variance was attributable to time-specific aetiological influences at  $t_2$ . At  $t_3$ , 79% of genetic variance, 92% of shared environmental variance and 84% of non-shared environmental variance was attributable to time-specific aetiological influences (Table 5). For Raven's scores, 58% of genetic variance, 0% of shared environmental variance and 78% of non-shared environmental variance was attributable to time-specific aetiological influences at  $t_2$ . At  $t_3$ , 53% of genetic variance, 67% of shared environmental variance and 64% of non-shared environmental variance was attributable to time-specific aetiological influences (Table 6). Thus, many new genetic and environmental influences on ADHD symptoms, vocabulary and Raven's scores emerged at  $t_2$  and  $t_3$ , which were not explained by environmental or shared influences at  $t_1$  or  $t_2$  respectively.

**Table 4. Proportions of the phenotypic correlations between ADHD symptoms and Raven's Standard Progressive Matrices scores due to genetic (A), shared environmental (C) and non-shared environmental (E) influences.**

$r_{ph}$	Time 1	Time 2		Time 3	
	-0.21	-0.22		-0.22	
% of $r_{ph}$ due to		Total <sup>a</sup>	Time-specific <sup>b</sup>	Total <sup>a</sup>	Time-specific <sup>b</sup>
<b>A</b>	81% (0.17)	77% (0.17)	36% (0.08)	68% (0.15)	32% (0.07)
<b>C</b>	5% (0.01)	0% (0.00)	0% (0.00)	0% (0.00)	0% (0.00)
<b>E</b>	14% (0.03)	23% (0.05)	14% (0.03)	32% (0.07)	23% (0.05)

ADHD = attention deficit hyperactivity disorder;  $r_{ph}$  = phenotypic correlation

<sup>a</sup>Proportions of the phenotypic correlation due to total genetic or environmental influences (i.e. transmitted plus age-specific effects).

<sup>b</sup>Proportions of the phenotypic correlation due to time-specific genetic or environmental influences specific to early adolescence.

Figures in parentheses refer to the absolute contributions of A, C and E respectively to the phenotypic correlations between ADHD symptoms and Raven's scores.

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**Table 5. Transmission of genetic (A), shared environmental (C) and non-shared environmental (E) influences between ADHD symptoms and vocabulary scores over time.**

	Time 2			Time 3		
ADHD symptoms	A	C	E	A	C	E
Total ACE variance	0.75	0.03	0.22	0.65	0.11	0.24
Proportion of total ACE variance due to						
ADHD symptoms (stability effect)	0.45 (60%)	0.02 (67%)	0.10 (45%)	0.40 (62%)	0.02 (18%)	0.12 (50%)
Vocabulary scores (cross-lagged effect)	0.00 (0%)	0.00 (0%)	0.00 (0%)	0.00 (0%)	0.00 (0%)	0.00 (0%)
Covariation between ADHD symptoms and Vocabulary scores (common effects)	0.01 (1%)	0.00 (%)	0.00 (%)	0.01 (2%)	0.00 (%)	0.00 (%)
Time-specific influences	0.29 (39%)	0.01 (33%)	0.12 (55%)	0.24 (36%)	0.09 (82%)	0.12 (50%)
Vocabulary scores	A	C	E	A	C	E
Total ACE variance	0.28	0.09	0.63	0.24	0.13	0.63
Proportion of total ACE variance due to						
Vocabulary scores (stability effect)	0.06 (21%)	0.03 (33%)	0.12 (19%)	0.04 (17%)	0.01 (8%)	0.10 (16%)
ADHD symptoms (cross-lagged effect)	0.02 (7%)	0.00 (0%)	0.00 (0%)	0.01 (4%)	0.00 (0%)	0.00 (0%)
Covariation between ADHD symptoms and Vocabulary scores (common effects)	0.01 (4%)	0.00 (0%)	0.00 (0%)	0.00 (0%)	0.00 (0%)	0.00 (0%)
Time-specific influences	0.19 (68%)	0.06 (67%)	0.51 (81%)	0.19 (79%)	0.12 (92%)	0.53 (84%)

Note: Percentages in parentheses refer to the proportion of variance at the age indicated transmitted from the previous time point, i.e. transmitted from time 1 to time 2 and from time 2 to time 3. For each trait, percentages within each column add up to 100%, and, thus, may not perfectly correspond to proportions derivable from parameter estimates in this table, due to rounding error.

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Of the 61% of the phenotypic correlation between ADHD symptoms and vocabulary scores at  $t_2$  that is due to genetic influences, a proportion of 30% was due to time-specific genetic influences at  $t_2$ , while the remaining 31% were due to lasting genetic influences transmitted from  $t_1$  (Table 3;  $30\% + 31\% = 61\%$ ). At  $t_3$ , 25% of the phenotypic correlation between ADHD symptoms and vocabulary scores were due to time-specific genetic influences, while the remaining 25% were due to lasting genetic influences transmitted from  $t_2$ . A proportion of 9% of the phenotypic correlation between ADHD symptoms and vocabulary scores was due to time-specific shared environmental influences at  $t_2$ , while the remaining 8% were due to lasting shared environmental influences transmitted from  $t_1$ . At  $t_3$ , 12.5% of the phenotypic correlation between ADHD symptoms and vocabulary scores were due to time-specific shared environmental influences, while the remaining 12.5% were due to lasting shared environmental influences transmitted from  $t_2$ . A proportion of 13% of the phenotypic correlation between ADHD symptoms and vocabulary scores was due to time-specific non-shared environmental influences at  $t_2$ , while the remaining 9% were due to lasting non-shared environmental influences transmitted from  $t_1$ . At  $t_3$ , 25% of the phenotypic correlation between ADHD symptoms and vocabulary scores were due to time-specific non-shared environmental influences, while the remaining 12.5% were due to lasting non-shared environmental influences transmitted from  $t_2$ .

Of the phenotypic correlation between ADHD symptoms and Raven's scores at  $t_2$ , 36% were due to time-specific genetic influences at  $t_2$ , whereas the remaining 41% were due to lasting genetic influences transmitted from  $t_1$  (Table 4). At  $t_3$ , 32% of the phenotypic correlation between ADHD symptoms and Raven's scores was due to time-specific genetic influences, whereas the

**Table 6. Transmission of genetic (A), shared environmental (C) and non-shared environmental (E) influences between ADHD symptoms and Raven's Standard Progressive Matrices over time.**

	Time 2			Time 3		
ADHD symptoms	A	C	E	A	C	E
Total ACE variance	0.78	0.10	0.20	0.71	0.06	0.23
Proportion of total ACE variance due to						
ADHD symptoms (stability effect)	0.47 (60%)	0.02 (20%)	0.09 (45%)	0.45 (63%)	0.01 (17%)	0.09 (39%)
Raven's scores (cross-lagged effect)	0.01 (1%)	0.01 (10%)	0.01 (5%)	0.00 (0%)	0.00 (0%)	0.00 (0%)
Covariation between ADHD symptoms and Raven's scores (common effects)	0.01 (1%)	0.00 (0%)	0.00 (0%)	0.01 (1%)	0.00 (0%)	0.00 (0%)
Time-specific influences	0.29 (38%)	0.07 (70%)	0.10 (50%)	0.25 (36%)	0.05 (83%)	0.14 (61%)
Raven's scores	A	C	E	A	C	E
Total ACE variance	0.31	0.04	0.59	0.30	0.06	0.64
Proportion of total ACE variance due to						
Raven's scores (stability effect)	0.11 (36%)	0.04 (100%)	0.13 (22%)	0.12 (40%)	0.02 (33%)	0.23 (36%)
ADHD symptoms (cross-lagged effect)	0.01 (3%)	0.00 (0%)	0.00 (0%)	0.00 (0%)	0.00 (0%)	0.00 (0%)
Covariation between ADHD symptoms and Raven's scores (common effects)	0.01 (3%)	0.00 (0%)	0.00 (0%)	0.02 (7%)	0.00 (0%)	0.00 (0%)
Time-specific influences	0.18 (58%)	0.00 (0%)	0.46 (78%)	0.16 (53%)	0.04 (67%)	0.41 (64%)

Note: Percentages in parentheses refer to the proportion of variance at the age indicated transmitted from the previous time point, i.e. transmitted from time 1 to time 2 and from time 2 to time 3. For each trait, percentages within each column add up to 100% and, thus, may not perfectly correspond to proportions derivable from parameter estimates in this table, due to rounding error.

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remaining 36% were due to lasting genetic influences transmitted from  $t_2$ . At  $t_2$  and  $t_3$ , there were no shared environmental influences on the phenotypic correlation between ADHD symptoms and Raven's scores. A proportion of 14% of the phenotypic correlation between ADHD symptoms and Raven's scores was due to time-specific non-shared environmental influences at  $t_2$ , while the remaining 9% were due to lasting non-shared environmental influences transmitted from  $t_1$ . At  $t_3$ , 23% of the phenotypic correlation between ADHD symptoms and Raven's scores were due to time-specific non-shared environmental influences, while the remaining 9% were due to lasting non-shared environmental influences transmitted from  $t_2$ .

Overall, these results indicate that both stable aetiological factors and time-specific genetic and environmental influences emerging for *each trait* at  $t_2$  and  $t_3$  (Tables 5 and 6) are involved in the *association* between ADHD symptoms and vocabulary scores and the *association* between ADHD symptoms and Raven's scores across time.

### Phenotypic cross-lagged effects

All cross-lagged paths were small (Figs 2 and 3). This is a common finding [16,35–37], because cross-lagged paths are partial regression coefficients (i.e. they explain the left-over variance once the within-trait across-time stability has been accounted for). The full predictive relationships between ADHD symptoms and the two indicators of IQ (vocabulary and Raven's scores) are stronger, as indicated by the phenotypic correlations (Tables 1 and 2 respectively).

The stability paths of ADHD symptoms ( $b_{11} = 0.75$ ,  $b_{22} = 0.73$ ) and vocabulary scores ( $b_{33} = 0.46$ ,  $b_{44} = 0.39$ ) were significant and moderate to high (Fig 2). All cross-lagged effects from



ADHD symptoms to vocabulary scores, and vice versa, were significant, as shown by the 95% confidence intervals. A  $\chi^2$ -test indicated that the cross-lagged path from ADHD symptoms at  $t_1$  to vocabulary scores at  $t_2$  ( $b_{12} = -0.14$ ) was significantly larger than the cross-lagged path from vocabulary scores at  $t_1$  to ADHD symptoms at  $t_2$  ( $b_{21} = -0.04$ ;  $\chi^2 = 67.76$ ,  $p < 0.001$ ,  $df = 1$ ). The cross-lagged path from ADHD symptoms at  $t_2$  to vocabulary scores at  $t_3$  ( $b_{34} = -0.10$ ) was not significantly different from the cross-lagged path from vocabulary scores at  $t_2$  to ADHD symptoms at  $t_3$  ( $b_{43} = -0.07$ ;  $\chi^2 = 2.30$ ,  $p = 0.13$ ,  $df = 1$ ). Analyses of the relationship between vocabulary and inattention scores, and the relationship between vocabulary and hyperactivity-impulsivity scores, revealed the same pattern as above for both symptom dimensions (not presented here).

In the cross-lagged model of the association between ADHD symptoms and Raven's scores, the stability paths of ADHD symptoms ( $b_{11} = 0.76$ ,  $b_{22} = 0.76$ ) and Raven's scores ( $b_{33} = 0.52$ ,  $b_{44} = 0.61$ ) were similarly significant and moderate to high (Fig 3). All cross-lagged effects from ADHD symptoms to Raven's scores, and vice versa, were significant, as shown by the 95% confidence intervals. A  $\chi^2$ -test indicated that the cross-lagged path from ADHD symptoms at  $t_1$  to Raven's scores at  $t_2$  ( $b_{12} = -0.10$ ) was significantly larger than the cross-lagged path from Raven's scores at  $t_1$  to ADHD symptoms at  $t_2$  ( $b_{21} = -0.05$ ;  $\chi^2 = 15.19$ ,  $p < 0.001$ ,  $df = 1$ ). The cross-lagged path from ADHD symptoms at  $t_2$  to Raven's scores at  $t_3$  ( $b_{34} = -0.08$ ) was not significantly different from the cross-lagged path from Raven's scores at  $t_2$  to ADHD symptoms at  $t_3$  ( $b_{43} = -0.04$ ;  $\chi^2 = 2.36$ ,  $p = 0.09$ ,  $df = 1$ ). Analyses of the relationship between Raven's and inattention scores, and the relationship between Raven's and hyperactivity-impulsivity scores, revealed the same pattern as above for both symptom dimensions (not presented here).

## Discussion

In this cross-lagged analysis exploring the developmental patterns of the causal directions and the aetiology of the association between ADHD symptoms and IQ, three key findings emerged that together shed light on the aetiology of the longitudinal relationship between ADHD symptoms and IQ in the general population.

Firstly, time-specific genetic and environmental influences emerged for *each trait* at  $t_2$  and  $t_3$ . Yet, heritabilities remained high for ADHD and moderate for vocabulary and Raven's scores across the three time points. This finding suggests that ADHD and IQ are developmentally complex phenotypes characterised by both continuity and change of the aetiological influences across adolescence. The stable and dynamic nature of the genetic risks supports a "developmentally dynamic" hypothesis of ADHD [38]. Considering ADHD in a developmental framework implies that early intervention could help to reduce ADHD symptoms, as well as the impact these symptoms may have on IQ. Future research should investigate the developmental patterns of the association between ADHD symptoms and IQ at earlier as well as later stages of development.

Secondly, we found that the (genetic) association of ADHD symptoms with vocabulary and Raven's scores at  $t_2$  and  $t_3$  were determined by both time-specific genetic and environmental influences emerging for *each trait* at  $t_2$  and  $t_3$  and the associations transmitted from previous time points. Thus, the aetiological factors involved in the *association* of ADHD symptoms with vocabulary and Raven's scores were moderately stable across time points, despite the large sample and, thus, increased power to detect time-specific aetiological influences. The stable aetiological influences on the association of ADHD symptoms with IQ may indicate that enduring molecular, and hence neurobiological, processes play an important role for the

association. Future research should explore these processes, for example through molecular genetic, neuropsychological and neuroimaging studies.

Thirdly, ADHD symptoms and vocabulary scores, and ADHD symptoms and Raven's scores, significantly predicted each other from  $t_1$  to  $t_2$  and from  $t_2$  to  $t_3$ . However, ADHD symptoms at  $t_1$  were a significantly stronger predictor of both vocabulary and Raven's scores at  $t_2$  than vice versa. No differential effects emerged for the cross-lagged paths from ADHD symptoms at  $t_2$  to vocabulary or Raven's scores at  $t_3$  and vice versa. The lack of differential effects may be explained by the fact that the direct effects of ADHD symptoms at  $t_2$  on vocabulary or Raven's scores at  $t_3$  and vice versa are likely attenuated by the indirect effects from the associations at previous time points (which also explain the relationships). The developmental patterns for the association of ADHD symptoms with these two IQ subscales were highly comparable.

The cross-lagged effects are small, as is common [16,35–37], because cross-lagged paths explain the left-over variance once the within-trait across-time stability has been accounted for. As indicated by the phenotypic correlations, the full predictive relationships between ADHD symptoms and the two indicators of IQ (vocabulary and Raven's scores) are stronger than the cross-lag estimates. The significant negative cross-lagged associations between ADHD symptoms and the two IQ subscales, therefore, suggest ADHD symptoms could contribute to an increased risk for worse life outcomes, as IQ has previously been shown to predict overall outcome in individuals with ADHD [10,11] and is also a good predictor of life success in the general population, predicting, for example, educational achievement and longevity [12,13]. Contrary to studies investigating VIQ and PIQ in individuals diagnosed with ADHD [3–5], no differential effects emerged for VIQ and PIQ in our population-based twin sample. Future research will have to substantiate these findings in the general population and in individuals diagnosed with ADHD in order to establish potential cognitive strengths and weaknesses associated with ADHD to guide treatment and educational programmes.

One way in which ADHD symptoms may affect IQ scores is through education: the core symptoms of ADHD—inattention, impulsivity and hyperactivity—may lead to difficulties in following teachers' instructions and lesson content and, thus, interfere with opportunities to benefit from education. Data from the prospective, population-based Avon Longitudinal Study of Parents and Children ( $n = 11,640$ ) show that parent-rated hyperactivity and inattention symptoms measured at age 3 had negative effects on academic outcomes at age 16 [39]. Furthermore, ADHD symptoms were found to negatively affect academic achievement concurrently and longitudinally (after 5 years) in 192 12-year olds from the general population [40]. These studies suggest that high levels of ADHD symptoms predict poor academic outcomes and lower levels of education, which in turn have been associated with lower scores on Wechsler intelligence subtests [41]. Recent research also suggests that the Raven's Progressive Matrices test is influenced by education [42,43]. Education may, thus, be a putative mechanism via which ADHD symptoms affects IQ scores in the way our results suggest.

The study has some limitations. We investigated the association between ADHD symptoms and IQ in a population-based sample of twins rather than a clinical sample. The associations of ADHD symptoms with VIQ and PIQ are likely to be greater and may differentiate in individuals diagnosed with ADHD [3,4]. However, examining large unselected population samples decreases the risk of possible selection biases associated with clinical samples. Secondly, the heritability estimates for the IQ subscales are lower than previously reported heritability estimates of general cognitive abilities ( $g$ ). This may be because  $g$  is a latent trait generated from multiple measures and here, we separately analysed vocabulary and Raven's scores as proxies for VIQ and PIQ. In a genome-wide complex trait analysis of this sample the typical pattern of genetic stability and increasing heritability for  $g$  were found, with DNA-estimated heritabilities

increasing from 0.26 at age 7 to 0.45 at age 12 years, [44]. Thirdly, there was a change in the specific test used to measure vocabulary from age 14 to 16 years. Yet, the test conducted at age 16 was analogous to the test conducted at ages 12 and 14 years; in both the participant's task was to select the correct synonym for a word from a list of alternatives. Their similarity is reflected in the comparable magnitudes of the stability paths from ages 12–14 years and ages 14–16 years. Lastly, while a cross-lag model may allow us to examine the direction of effects, further research is required to draw firm conclusions about the direction of causality.

These limitations notwithstanding, the prospective developmental design of our cross-lagged analysis allowed us to explore the direction of effects for the negative association between ADHD symptoms and IQ scores, as well as the dynamic and stable nature of the aetiological influences on these variables and their association. ADHD symptoms and IQ scores significantly predicted each other over time. Yet, ADHD symptoms at age 12 years were a significantly stronger predictor of both vocabulary and Raven's scores at age 14 years than vice versa. Time-specific aetiological influences emerged for each trait. However, the aetiological factors involved in the association between ADHD symptoms and IQ were highly stable over time. Future research will need to build on these results to investigate how early intervention targeting ADHD symptoms may aid in reducing the risk for lower IQ.

## Supporting Information

**S1 Dataset. Data from the Twins Early Development Study: ADHD symptom ratings, Vocabulary and Raven's Progressive Matrices score at age 12, 14 and 16.**  
(CSV)

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## Author Contributions

Conceived and designed the experiments: AR FR. Analyzed the data: AR FR. Contributed reagents/materials/analysis tools: FR CG. Wrote the paper: AR FR CG PA JK.

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## **Chapter 6. Is Physical Activity Causally Associated With Symptoms of ADHD?**

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# Is Physical Activity Causally Associated With Symptoms of Attention-Deficit/Hyperactivity Disorder?

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**Objective:** Emerging evidence suggests that physical activity (PA) enhances cognition and may be a protective factor for attention-deficit/hyperactivity disorder (ADHD). Yet the impact of PA on ADHD symptoms has been investigated only in a few undersized, non-randomized, and retrospective studies. We examined the effect of PA during late adolescence on ADHD symptoms in early adulthood while controlling for unmeasured genetic and shared environmental confounding.

**Method:** The effect of PA at age 16 to 17 years (baseline) on ADHD symptoms at age 19 to 20 years (follow-up) was examined using a within-monozygotic (MZ) twins fixed-effects model in 232 MZ twin pairs born in Sweden between May 1985 and December 1986. Parents rated their children's DSM ADHD symptoms at baseline and follow-up. Participants' weekly energy expenditure (in metabolic equivalent task minutes per week) was based on self-reports at baseline of PA frequency, intensity, and duration.

**Results:** Greater weekly energy expenditure in adolescence was significantly associated with reduced ADHD

symptom levels in early adulthood, even when controlling for unmeasured confounding (all genetic and environmental factors shared within MZ twin pairs) as well as ADHD symptoms and body mass index (BMI) at baseline,  $\beta = -0.21$ ,  $p = .013$  (95% CI =  $-0.38$  to  $-0.05$ ). Similar results were observed for the 2 ADHD subcomponents: hyperactivity/impulsivity,  $\beta = -0.21$ ,  $p = .022$  (95% CI =  $-0.39$  to  $-0.03$ ), and inattention,  $\beta = -0.19$ ,  $p = .049$  (95% CI =  $-0.36$  to  $-0.0005$ ).

**Conclusion:** In line with a causal hypothesis, PA was inversely associated with ADHD symptoms, even after adjusting for unmeasured confounding. These findings suggest that PA in adolescence might decrease ADHD symptoms in early adulthood. However, given the size of the effect, the clinical value of this intervention needs to be explored further.

**Key Words:** physical activity, ADHD, exercise, twin modeling, TCHAD

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Attention-deficit/hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder characterized by developmentally inappropriate and impairing levels of hyperactivity, impulsivity, and/or inattention.<sup>1</sup> Both the symptoms and functional impairments associated with ADHD persist from childhood into adolescence and adulthood in around 65% of individuals with the disorder.<sup>2</sup> Across the lifespan, ADHD is associated with a significant risk of lower academic and occupational achievement,<sup>3</sup> interpersonal problems, mental illness, and delinquency.<sup>4</sup> Multimodal treatment plans including psychostimulant medication, non-psychostimulant medication, and psychological interventions, tailored to the specific needs of the patient, are recommended for the treatment of ADHD.<sup>5</sup> Because of their persistence, there is a continued need for treatment and management of ADHD symptoms and impairments from childhood through adolescence and into adulthood.

A robust evidence base stemming from randomized controlled trials attests to the efficacy of psychostimulant and nonpsychostimulant medication in reducing the

symptoms of ADHD.<sup>6</sup> Yet treatment with medication has its limitations. Some individuals may not respond to medication, and complete normalization of symptoms is rare.<sup>7</sup> Medication may be less effective for treating associated impairments of ADHD, such as poor social skills<sup>8</sup> and executive function (EF) deficits,<sup>9</sup> and its long-term effectiveness for control of ADHD symptoms and impairments is yet to be established.<sup>10</sup> Adverse side effects on sleep, appetite, and growth are also possible.<sup>11</sup> Furthermore, some patients, parents, and clinicians have reservations about medication use,<sup>12</sup> and the majority of individuals who are prescribed medication stop taking it within the first year.<sup>13</sup> These potential problems are acknowledged by the National Institute for Health and Care Excellence (NICE) clinical guidelines, which recommend that nonmedical interventions should be considered as possible first-line treatment where ADHD is associated with moderate levels of impairment.<sup>5</sup>

A variety of nonpharmacological interventions, such as psychological (cognitive training, neurofeedback, and behavioral training) and dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) interventions, are also available. A recent meta-analysis found blinded evidence that behavioral interventions used to treat children and adolescents with ADHD had beneficial effects on important aspects of child



This article is discussed in an editorial by Dr. Jeffrey M. Halperin on page 537.

and parent functioning, namely decreasing comorbid childhood conduct problems and increasing positive parenting.<sup>14</sup>

Yet the evidence for the efficacy of nonpharmacological treatment interventions on reducing ADHD symptoms is far from clear and is limited by the unblind status of researchers and raters of behavior, as another recent meta-analysis by the same group concluded.<sup>15</sup> Blinded evidence for small but significant reductions in ADHD symptoms was found only for free fatty acid supplementation and artificial food color exclusion.<sup>15</sup>

Identifying new nonpharmacological treatments on the basis of our growing understanding of the pathophysiology as well as risk and protective factors of ADHD would therefore be a significant advance in the management of ADHD. Animal research and studies in typically developing children, adolescents, and adults suggest physical activity (PA) and exercise as a putative treatment target, potentially diminishing an individual's level of ADHD symptoms and associated impairments.<sup>16</sup> Here, PA is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, whereas exercise is a subcategory of PA that is planned, structured, repetitive, and purposeful. Yet more and better-quality evidence is needed to establish the impact of PA on ADHD symptoms and its efficacy in alleviating the symptoms and impairments associated with the disorder.

Findings from a study investigating the correlation between cognitions and exercise quantity are consistent with the notion that PA may be beneficial for individuals with high levels of ADHD symptoms and associated impairments. Exercise quantity was measured each day over a period of 1 week using an accelerometer in 18 boys diagnosed with ADHD. The study found that exercise quantity was significantly correlated with working memory, inhibition, and information processing.<sup>17</sup> Yet the correlational and nonrandomized design prohibits causal interpretations and limits conclusions about efficacy.

A study assessing the effects of a 10-week moderate-to-high-intensity exercise program on fitness, cognitive functioning, and ADHD-related behavior in 10 children with ADHD, compared to a no-intervention control group consisting of 11 children with ADHD, reported significant improvements in muscular capacities, motor skills, level of information processing, and parent- and teacher-rated social, thought, and attention problems following the intervention.<sup>18</sup> No information is available as to whether this study was randomized and blinded.

Three studies investigating the effect of PA in individuals with ADHD have used a randomized prospective design. One of these studies examined the effects of acute exercise on EF.<sup>19</sup> Thirty minutes of moderate-intensity running facilitated selective attention, processing speed, and set-shifting in 20 children with ADHD who were randomly assigned to the PA group, relative to 20 children with ADHD assigned to the control condition of watching a PA-related video.<sup>19</sup> The second study explored the association between chronic PA and attention in 84 children with ADHD. Compared to individuals who did not receive an intervention, individuals randomly assigned to a moderate-intensity

10-week exercise program of 3 sessions per week improved on teacher ratings of attention, motor skills, and academic and classroom behavior.<sup>20</sup> In the third randomized study, teacher-rated cooperativeness and EF, as indicated by the digit symbol test, were significantly improved by 12 bi-weekly exercise sessions, relative to behavioral educational sessions, in 28 boys with ADHD.<sup>21</sup> Although no significant changes were found with regard to hyperactivity scores, inattention scores improved in the exercise group. These randomized prospective studies thus suggest that PA has positive effects on EF and behavioral symptoms associated with ADHD. Yet none of these studies established whether any short-term effects of PA were followed by longer-term benefits. Furthermore, none of these studies elaborate on the blinding status of the researchers and informants.

The findings from the studies reviewed above provide some support for the hypothesis that exercise has the potential to act as a protective factor for ADHD symptoms and associated impairments. Yet, concluding causality from nonrandomized, retrospective, and cross-sectional data is problematic. The studies looking at case-control differences are limited by inadequate control conditions, and the results may therefore be confounded by unmeasured genetic and environmental factors that may lead to spurious associations. The nonblinded status of the researchers and raters of behavior may further inflate the positive effects of exercise on the various outcome variables due to the nonspecific effects evoked by a child's participation in a treatment program.<sup>16</sup> Furthermore, little is known about the developmental influence of PA on ADHD symptoms. The purpose of this study was to examine the effect of PA during late adolescence on ADHD symptoms in early adulthood. Both the symptoms and functional impairments associated with ADHD often persist from childhood into adolescence and adulthood.<sup>2</sup> Although attention problems remain relatively stable, symptoms of hyperactivity and impulsivity tend to decline with age.<sup>22</sup> PA may thus be particularly beneficial for the age group examined here, as PA seems to affect inattention more than hyperactivity/impulsivity symptoms.<sup>18,20,21</sup> In light of these findings, the impact of PA on ADHD symptoms is examined together and separately for the 2 subcomponents of ADHD, inattention and hyperactivity/impulsivity. Investigating the effect in 232 monozygotic (MZ) twin pairs enables us to control for unmeasured genetic and shared environmental confounding factors that may influence the relationship between PA and ADHD symptoms, allowing us to draw tentative causal inferences about this relationship.

## METHOD

### Sample

Data came from the Swedish Twin Study of CHild and Adolescent Development (TCHAD). TCHAD is an ongoing prospective longitudinal twin study concerning health and behavior in twins from childhood to early adulthood.<sup>23</sup> The study is a subsample of the Swedish Twin Registry and contains about 1,450 twin pairs born in Sweden between May 1985 and December 1986. The twins and their parents have been contacted on 4 different occasions using postal questionnaires. The current study used data from waves 3 and 4.



The TCHAD sample is representative of the Swedish population with regard to educational level and employment status but not ethnicity.<sup>23</sup> In wave 3, the response rate was 74% for parents ( $n = 1,067$ ), and 82% for twins ( $n = 2,369$ ). In wave 4, parents' response rate was 40% ( $n = 1,158$ ), and the twins' response rate was 59% ( $n = 1,705$ ).<sup>24</sup> The zygosity of 1,312 twins was confirmed by DNA test during wave 4 when all twins were asked to provide a DNA sample with the help of OraGenes DNA (DNA Genotek Inc., Ottawa, ON, Canada) self-collection kits. For 1,444 twins without a DNA sample, zygosity was determined based on an algorithm derived from discriminant analyses of twins' and parents' responses to validated questionnaires.<sup>23</sup> In cases of any contradictions between the assignments ( $n = 100$ , 3.4%), the zygosity was set to unknown, and the twins were excluded from the analyses. The present study included 232 monozygotic (MZ) twin pairs who had completed self-report measures on PA at age 16 to 17 years and whose parents had completed parent-report measures of ADHD symptoms at ages 16 to 17 and 19 to 20 years. The included MZ twins did not differ significantly from the individuals lost to follow-up with regard to physical activity levels ( $t = -0.53$ ,  $df = 767$ ,  $p = .60$ ), ADHD symptoms in adolescence ( $t = -0.25$ ,  $df = 839$ ,  $p = .80$ ), and ADHD symptoms in early adulthood ( $t = 0.69$ ,  $df = 497$ ,  $p = .49$ ). Approximately half (48.74%) of the participants were male. Ethical approval was obtained from the Ethics Committee of the Karolinska Institute, Stockholm, Sweden. No informed consent was required because, according to Swedish regulations, response to the questionnaire constitutes consent.<sup>24</sup>

## Measures

PA is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. PA is a complex and multidimensional exposure, and, when assessing its effect, the intensity, duration, and frequency with which it is performed must be taken into account.<sup>25</sup> The twins provided self-ratings of their PA by answering 3 multiple-choice questions enquiring about the intensity, frequency, and duration of their leisure-time PA (Table 1). The intensity indicated by the participant was converted into metabolic equivalents of task (MET) using the Compendium of Physical Activities.<sup>26</sup> The average duration per PA session indicated by the participant was converted into minutes per session, respectively. PA frequency was converted into PA sessions per week. Weekly energy expenditure (EE) of PA was then calculated using the following formula, where higher scores indicate greater PA<sup>27</sup>:

$$\begin{aligned} &\text{Intensity (MET)} \times \text{Duration (min/time)} \\ &\quad \times \text{Frequency (times/week)} \\ &= \text{weekly EE (MET} \cdot \text{min/week)}. \end{aligned}$$

At age 16 to 17 years, parents completed a binary-coded checklist (0 = not true, 1 = true) of 14 ADHD symptom items based on *DSM-IV* criteria.<sup>28</sup> Because of the changes in the *DSM* during the follow-up period of the TCHAD study, the full set of all 18 *DSM-IV* ADHD symptoms was not included.<sup>29</sup> At age 19 to 20 years, parents provided ratings of their children's ADHD symptoms based on the 18 *DSM-IV* items for ADHD<sup>28</sup> via a Likert-type scale (0 = not true; 1 = sometimes true; 2 = often true). At both time points, parents were asked to check symptoms persisting for at least 6 months. Separate scores for inattention and hyperactivity/impulsivity as well as a total *DSM-IV* ADHD symptom score were established from these ratings. Higher scores indicate greater symptom severity.

Participants also provided their weight (in kilograms [kg]) and height (in meters [m]) at baseline. Each participant's body mass index (BMI) was calculated by dividing his/her body weight in kilograms by his/her height in meters squared ( $\text{kg/m}^2$ ). Descriptive statistics for these variables can be found in Table 2.

**TABLE 1** Physical Activity Questionnaire Enquiring About the Intensity, Frequency, and Duration of the Participant's Leisure-Time Physical Activity

Question 1	How often do you exercise or play sports in your spare time?
Answers	1. Never 2. Less than once a month 3. 1–2 times a month 4. About once a week 5. 2–3 times a week 6. 4–5 times a week 7. Almost every day
Question 2	The intensity of your exercise is comparable to:
Answers	1. Walking 2. Walking/jogging 3. Jogging 4. Running
Question 3	On average, how long are your exercise sessions?
Answers	1. Shorter than half an hour 2. Half an hour to less than 1 hour 3. One hour to less than 2 hours 4. Two hours or more

## Statistical Analysis

The relationship between PA and ADHD symptoms was investigated using a within-MZ twins fixed-effect model,<sup>30</sup> which models within-MZ twin pair differences in ADHD symptoms as a function of within-pair differences of weekly EE. Thus, the analysis allows the effect of PA on ADHD symptom levels to be estimated while accounting for unmeasured confounding factors (i.e., all genetic and environmental factors shared within MZ twin pairs). This is due to the fact that MZ twins share 100% of their inherited DNA sequence and are expected to share many aspects of their environment by virtue of being born at the same time and place and growing up in the same family. As ADHD symptoms and BMI<sup>31</sup> at baseline were likely to be important confounders for the estimated effect of weekly EE on ADHD symptoms at follow-up, we included them in the model. Weekly EE and ADHD symptoms were studied as continuous variables. Models were fitted to standardized ( $z$ ) weekly EE and ADHD symptom scores. Analyses were performed separately for inattentive, hyperactive/impulsive, and total ADHD symptoms. All analyses were conducted in Stata 13 software.

## RESULTS

The within-MZ twins, fixed-effect model revealed that greater weekly EE at age 16 to 17 years significantly predicted reduced ADHD symptoms at age 19 to 20 years ( $\beta = -0.30$ ,  $p < .001$ , 95% CI =  $-0.46$  to  $-0.15$ ). Greater weekly EE at age 16 to 17 years significantly predicted reduced ADHD symptoms at age 19 to 20 years even when controlling for ADHD symptoms and BMI at baseline ( $\beta = -0.21$ ,  $p = .013$ , 95% CI =  $-0.38$  to  $-0.05$ ). Dimension-specific analyses indicated that, even when controlling for baseline BMI and hyperactivity/impulsivity and inattention symptom levels, respectively, greater weekly EE at age 16 to 17 years was significantly associated with reduced hyperactivity/impulsivity symptom levels at age 19 to 20 years ( $\beta = -0.21$ ,  $p = .022$ , 95% CI =  $-0.39$  to  $-0.03$ ), as well as with reduced inattention symptom levels at age 19 to 20

**TABLE 2** Descriptive Statistics for Raw (Nonstandardized) Scores

Characteristic	Mean	SD	Range
Weekly EE (MET-min/week) at age 16–17	44.47	30.46	0–153
Total ADHD symptoms at age 16–17	1.12	1.95	0–17
HI symptoms at age 16–17	0.32	0.88	0–9
IA symptoms at age 16–17	0.81	1.45	0–8
BMI at age 16–17	20.6	2.87	11.7–33.5
Total ADHD symptoms at age 19–20	2.50	3.48	0–28
HI symptoms at age 19–20	1.20	1.79	0–16
IA symptoms at age 19–20	1.30	2.18	0–18

Note: ADHD = attention-deficit/hyperactivity disorder; BMI = body mass index; EE = energy expenditure; HI = hyperactive/impulsive; IA = inattentive; MET-min/week = metabolic equivalent of task minutes per week; SD = standard deviation.

years ( $\beta = -0.19$ ,  $p = .049$ , 95% CI =  $-0.36$  to  $-0.0005$ ). Although the effect was slightly larger for hyperactivity/impulsivity symptoms, this difference was not significant, as indicated by the overlapping 95% CIs. Because the analyses were carried out using standardized ( $z$ ) scores, the  $\beta$  coefficients presented in this section represent a standardized effect size measure such that a 1-standard deviation change in EE leads to  $\beta$  change in standard deviation in ADHD symptoms. The effect size is comparable to Cohen's  $d$ .

## DISCUSSION

In the present study investigating the effect of PA on ADHD symptoms, higher levels of PA, indicated by higher weekly energy expenditure, in late adolescence were associated with lower ADHD symptom scores in early adulthood, even when adjusting for baseline ADHD symptoms, BMI, and unmeasured genetic and shared environmental confounding factors. These results are in line with a causal hypothesis, indicating that PA may represent a protective factor for ADHD. By using a longitudinal design and focusing on weekly energy expenditure rather than a particular kind of exercise, we demonstrated that PA might have long-term beneficial effects on ADHD symptoms. These findings, therefore, strengthen and extend the limited body of research conducted to date that suggests that PA improves symptoms and impairments associated with ADHD.<sup>16</sup>

Although previous research suggested a differential effect of PA on inattention and hyperactivity/impulsivity symptoms,<sup>18,20,21</sup> we found that PA in late adolescence had a positive impact on both inattention and hyperactivity/impulsivity symptom levels in early adulthood. Consequently, PA may offer benefits to individuals across development. As ADHD is often chronic, with prominent symptoms and impairment spanning from childhood into adolescence and adulthood,<sup>2</sup> these findings provide support for the idea that PA may represent a promising protective factor and treatment target for ADHD. The implementation of lifestyle changes in the form of more PA incorporated into daily routines, promoting an individual's physical health, behavior, and neuropsychological functioning, may have the potential for flattening the adverse trajectory of the disorder and yielding long-term improvements. However, the effect of PA on ADHD symptoms was small to moderate ( $-0.21$ )

in this population-based sample of twins, and further research is needed to firmly establish the positive effect of PA and its magnitude in clinical populations. Although the pathways via which PA may influence ADHD symptoms remain to be elucidated, the up-regulation of brain-derived neurotrophic factor (BDNF) is 1 potential mechanism by which PA could induce its positive effects on ADHD symptoms. However, the strength of the association between BDNF and ADHD in humans remains unclear.<sup>16</sup>

One limitation of this study lies in the use of continuous ADHD symptom ratings in a population-based sample rather than a focus on clinically diagnosed cases. Consequently, we cannot be certain that these findings will generalize to clinical populations of individuals diagnosed with ADHD, and no firm conclusions about the clinical utility of PA on ADHD can yet be drawn. Furthermore, the analysis yielded a small to moderate effect size ( $-0.21$ ) with uncertain impact on individuals with high levels of ADHD symptoms and impairments. However, the use of a large unselected sample may also be regarded as a strength because it decreases the risk of referral and selection biases associated with a clinical sample. Another limitation of this study is that we could not control for all factors that were not shared between the MZ twins and that may have influenced PA, ADHD symptoms, or the association between PA and ADHD symptoms. Yet we were able to adjust for all shared genetic and environmental factors as well as for ADHD symptom levels and BMI at baseline (2 potentially important unshared confounders of the association) by using fixed effects. The use of self-report to measure PA could be considered a limitation of our study<sup>32</sup> because individuals with high levels of ADHD symptoms might report less accurately on PA due to difficulties with time estimation, EF, and working memory. Yet this issue is likely to be less pronounced in our unselected general population sample. Furthermore, our measure of ADHD symptoms has not been formally validated. Although we used cross-informant data (i.e., parent-report for ADHD, self-report for PA), relying on a single source of informant (e.g., lack of teacher report) to assess ADHD symptoms may be regarded as another limitation. However, DSM-based parent-rating scales have been shown to predict interview-based diagnoses in childhood and adulthood with adequate sensitivities and specificities,<sup>33</sup> and our ADHD instrument has been used in several epidemiological studies previously and has reproduced several

well-established findings in the ADHD literature<sup>29,34-36</sup>. Finally, this study lacked a randomized prospective design. Future randomized control trials will therefore have to substantiate the potential of PA to act as a protective factor for ADHD.

In line with a causal hypothesis, PA was inversely associated with total ADHD, hyperactivity/impulsivity, and inattention symptoms, even after adjusting for unmeasured confounding factors, as well as ADHD symptom levels and BMI at baseline, indicating that PA may represent a protective factor for ADHD and a novel treatment target. Yet research into the efficacy of PA as an intervention for ADHD is in its infancy. Methodologically robust, blinded, randomized controlled trials using objective measures of PA are needed to investigate the effect of both acute and chronic PA on ADHD. In addition, prospective longitudinal studies are needed to establish whether any short-term effects are followed by longer-term benefits. In the future, the intensity, frequency, and duration of PA required to yield benefits for individuals with ADHD will need to be established. Whether PA lends itself to early intervention and prevention strategies also remains to be elucidated. Studies will need to affirm whether and to what extent factors such as age, fitness levels, or ADHD symptom severity affect who is likely to respond to a PA-based intervention. It remains to be seen what the mechanisms are that underlie the positive effect of PA on ADHD symptoms and how far the effect extends beyond the core symptoms of ADHD. *✉*

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## Chapter 7. General discussion and conclusions

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### 7.1 Summary of aims

The overall aim of this thesis was to study the association of attention-deficit/hyperactivity disorder (ADHD) with bipolar disorder (BD) and preterm birth, and to investigate the risk or protective factors IQ and physical activity (PA), using a combination of cognitive-neurophysiological and genetically-sensitive longitudinal designs. The objective of the first data-based chapter (chapter 2) of this thesis was a cross-disorder comparison between ADHD and BD. This cross-disorder comparison aimed to examine the cortical activity patterns that may underlie the symptom overlap between the two disorders using quantitative EEG (QEEG), in order to explore biomarkers, which may aid clinical differentiation of these disorders. The following two data-based chapters (chapters 3 and 4) aimed to investigate the cognitive-neurophysiological profile of adolescents born preterm using QEEG and ERP measures. By directly comparing the cognitive-neurophysiological profile of adolescents born preterm to the cognitive-neurophysiological profile of adolescents with ADHD and healthy controls, this thesis aimed to investigate whether the ADHD-like symptoms and cognitive impairments seen in preterm-born adolescents are identical to those linked to ADHD. In addition, chapters 3 and 4 aimed to examine the relationship of age with EEG spectral power and ERP components respectively in our sample of adolescents born preterm, term-born adolescents with ADHD and term-born controls. The next two data-based chapters then employed genetically-sensitive longitudinal designs to examine IQ and physical activity (PA) as risk and protective factors for ADHD. The aim of chapter 5 was to establish the developmental pattern of the association of ADHD symptoms with verbal and performance IQ and to examine the genetic and environmental aetiologies of the association of ADHD symptoms with verbal and performance IQ within time point, and their stability across time in a population-based twin sample. The final study (chapter 6) aimed to investigate the effect of PA during late adolescence on ADHD symptoms in early adulthood in a sample of monozygotic twins, while controlling for unmeasured genetic and shared environmental confounding factors that may influence the relationship between PA and ADHD symptoms. In this concluding chapter, the key findings of this

thesis will be summarised to draw together common themes and to link the findings to their wider implications for ADHD, BD and preterm birth. Strengths and limitations of the studies, as well as future directions, will also be outlined.

## **7.2 Key findings**

### ***7.2.1 Commonalities in EEG spectral power abnormalities between ADHD and bipolar disorder during rest and cognitive performance***

While ADHD and BD denote distinct psychiatric conditions, diagnostic delineation is impeded by considerable symptomatic overlap. Using a sample of 20 women with adult ADHD, 20 women with BD and 20 control women, we investigated whether QEEG identifies differences or similarities between women with ADHD and women with BD during resting-state and task conditions. Compared to controls, both ADHD and BD participants showed higher frontal theta power during the resting-state condition. No significant differences emerged between the two clinical groups. Whereas control participants demonstrated an increase in frontal theta power from rest to cognitive task condition, no task-related change in frontal theta power was found in the ADHD and BD groups. These findings suggest commonalities in brain dysfunction between ADHD and BD. Theta power may play a role as a marker of neurobiological processes in both disorders. Furthermore, this study was the first to investigate the EEG patterns during both rest and task conditions in women with adult ADHD. The results support previous research in an all-male sample, which showed no differences in cortical activation between controls and individuals with ADHD during the cognitive task and no change in spectral power from resting-state to cognitive task condition (Skirrow et al., 2015), suggesting that cortical activation patterns are similar in men and women with adult ADHD.

### ***7.2.2 Altered EEG spectral power in adolescents with ADHD and preterm born adolescents during rest and cognitive performance***

Similar to chapter 2, chapter 3 aimed to investigate the commonalities and differences in brain dysfunction between ADHD and preterm birth using quantitative EEG in adolescents born preterm, term-born adolescents with ADHD and term-born controls during resting-state and cognitive task conditions.

Preterm birth has been associated with a cognitive profile that resembles ADHD as well as with ADHD diagnosis per se. Few studies have directly compared individuals with ADHD and individuals born preterm on cognitive-neurophysiological measures. Consequently, chapter 3 aimed to examine if similarities or differences in cortical arousal emerge between adolescents with ADHD and adolescents born preterm during a resting-state condition with eyes open and a continuous performance test with flankers (CPT-OX). Delta power was the only frequency band to demonstrate a significant group-by-condition interaction. While the ADHD group did not differ significantly from the preterm and control groups during rest with regard to delta power, during CPT-OX the ADHD group showed significantly increased delta power compared to both the preterm and control groups. The preterm group did not differ significantly from the control group with regard to delta power during EO or CPT-OX. The group differences were likely driven by differences in rest-to-task transition effects between the groups, namely a significant increase in delta power from EO to CPT-OX in the ADHD and control groups, and no change in delta power from EO to CPT-OX in the preterm group. These results provide some of the first QEEG evidence for differences in oscillation patterns in the delta range, especially with regard to rest-to-task transition effects between term-born adolescents with ADHD and adolescents born preterm. In addition, this study did not replicate previous findings with regard to rest-to-task transition effects in adults with ADHD (Skirrow *et al.* 2015, chapter 2). In samples of men (Skirrow *et al.*, 2015) and women (chapter 2) with adult ADHD, we demonstrated that, compared to controls, theta power was significantly increased in individuals with ADHD during the resting-state condition but that theta did not differ between controls and individuals with ADHD during the CPT-OX. This pattern of findings was driven by a lack of change in EEG spectral power from resting-state to cognitive task condition in the ADHD group. Differences in sample ages may have contributed to the discrepancies between the current findings in adolescents (chapter 3) and previous findings in adults with ADHD (chapter 2; Skirrow *et al.*, 2015), as suggested by the current analysis (chapter 3), which demonstrated a negative moderate-to-large relationship of age with EEG spectral power in the delta bands across all three groups.



### ***7.2.3 Neurophysiological impairments of attention and inhibition: a comparison of adolescents with ADHD and adolescents born preterm***

To further investigate commonalities and differences in brain dysfunction between ADHD and preterm birth, the next study (chapter 4) compared ERP measures associated with attentional and inhibitory processing in adolescents with ADHD and adolescents born preterm. Impairments in attentional processing and response inhibition have previously been demonstrated in both individuals with ADHD and individuals born preterm but it remained unclear whether the impairments in individuals born preterm reflect identical impairments in individuals with ADHD. This chapter, therefore, aimed to establish whether the attention and inhibitory control impairments associated with preterm birth reflect identical neurophysiological impairments in term-born individuals with ADHD. Go-P3 amplitude was reduced, reflecting impaired response execution, in preterm-born adolescents compared to both control adolescents and adolescents with ADHD. Moreover, in adolescents born preterm CNV amplitude was attenuated, reflecting impairments in response preparation, compared to controls but not compared to adolescents with ADHD. The preterm group demonstrated significantly reduced NoGo-P3 amplitude, reflecting impaired response inhibition, compared to the control group at Cz but the two groups did not differ significantly at FCz. The preterm group further showed significantly increased NoGo-P3 amplitude compared to the ADHD group at FCz but not at Cz. Compared to the control group, NoGo-P3 amplitude was attenuated in the ADHD group at Cz but not at FCz. These findings indicate impairments in attentional orienting, response execution and response inhibition in adolescents born preterm. While some of the impairments found in adolescents born preterm overlap with those found in term-born adolescents with ADHD, the preterm group also showed unique deficits, suggesting that the deficits seen in the preterm group may be more wide-ranging than the deficits in the ADHD group.

### ***7.2.4 A longitudinal twin study of the direction of effects between ADHD symptoms and IQ***

As well as being associated with the specific cognitive impairments outlined above, ADHD symptoms are associated with overall lower general cognitive



ability (i.e. IQ scores). While the negative association between ADHD symptoms and IQ is well documented, our knowledge about the direction and aetiology of this association is limited. Making use of the genetic sensitivity and time-ordered nature of our twin data, we employed a cross-lagged model to explore the association of ADHD symptoms with verbal and performance IQ longitudinally in a population-based sample of 4,771 adolescent twin pairs. While time-specific aetiological influences emerged for each trait at ages 14 and 16 years, the aetiological factors involved in the association between ADHD symptoms and IQ were stable over time. ADHD symptoms and IQ scores significantly predicted each other over time. ADHD symptoms at age 12 years were a significantly stronger predictor of vocabulary and Raven's scores at age 14 years than vice versa, whereas no differential predictive effects emerged from age 14 to 16 years. These findings indicate that ADHD symptoms may put adolescents at risk for decreased IQ scores. Persistent genetic influences seem to underlie the association of ADHD symptoms and IQ over time.

### ***7.2.5 Is Physical Activity Causally Associated With Symptoms of ADHD?***

Emerging evidence suggests that PA enhances cognition and may be a protective factor for ADHD. Yet, the impact of PA on ADHD symptoms had been investigated only in a few undersized, non-randomised, and retrospective studies. We investigated the impact of PA (measured as weekly energy expenditure) during late adolescence on ADHD symptoms in early adulthood in 232 monozygotic twin pairs, while controlling for unmeasured genetic and shared environmental confounding using a within-monozygotic twins fixed-effects model. Greater weekly energy expenditure in adolescence was significantly associated with reduced ADHD symptom levels in early adulthood, even when controlling for all genetic and shared environmental factors shared within monozygotic (MZ) twin pairs, as well as ADHD symptoms and BMI at baseline. We found similar results for the two ADHD sub-components hyperactivity-impulsivity and inattention. These findings are in line with a causal relationship and suggest that PA in adolescence might decrease ADHD symptoms in early adulthood.

## **7.3 Wider implications**

ADHD is best conceptualised in a developmental framework (Frick & Nigg, 2012; Schmidt & Petermann, 2009). Although the supporting evidence is inconsistent (Cheung et al., 2015a; van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013), one neurodevelopmental model of ADHD views the disorder as resulting from early aberrations in brain development that remain relatively static throughout an individual's life. However, the plasticity of the brain and its interconnected neural circuits allow for recovery from ADHD symptoms and associated impairments over the course of development (Halperin & Schulz, 2006). Consequently, risk and protective factors may not only contribute to the initial development of the disorder, but may also play an important role in the developmental course and outcome of ADHD during adolescence and adulthood.

### ***7.3.1 Risk and protective factors***

While genetic factors play a key role in the susceptibility to ADHD (Burt, 2009; Wood, Buitelaar, et al., 2010), environmental factors also contribute to the development of the disorder and associated impairments (Thapar, Cooper, Jefferies, & Stergiakouli, 2012). The effects of genetic risks on development may depend on exposure to either adverse or enriched environments (Belsky & Pluess, 2009; Rutter, 2002), meaning that specific environmental factors may pose a risk for or provide protection from adverse long-term outcome in individuals with ADHD.

Chapter 4 provides evidence for response preparation and response inhibition impairments shared between adolescents born preterm and term-born adolescents with ADHD, suggesting that preterm birth may be a risk factor for ADHD. However, chapters 3 and 4 also demonstrated differences in neurophysiological impairments between term-born adolescents with ADHD and adolescents born preterm. In chapter 3, different cortical activation patterns in the delta band emerged between adolescents with ADHD and adolescents born preterm, especially with regard to rest-to-task transition effects. In addition, chapter 4 indicates a distinct impairment in response execution in adolescents born preterm, as well as a more frontally distributed NoGo-P3 component,

reflecting response inhibition, compared to term-born adolescents with ADHD. These differences in neurophysiological impairments between term-born adolescents with ADHD and adolescents born preterm may indicate more wide-ranging deficits in the preterm group. This idea is supported by research suggesting that, as well as being a risk factor for ADHD, preterm birth represents a risk factor for other psychiatric disorders, such as schizophrenia, bipolar disorder and autism spectrum disorder (D'Onofrio et al., 2013; Johnson & Marlow, 2014; Moster et al., 2008; Treyvaud et al., 2013). The late third trimester (32–40 weeks' gestation) serves as a critical period to lay the foundation of vital brain networks (Ball et al., 2014; van den Heuvel et al., 2014). It is, therefore, conceivable that preterm birth may result in trauma to the brain networks associated with ADHD, as well as other networks associated with additional impairments. These results, and the findings that ADHD symptom scores are increased in the preterm group compared to controls, suggest that preterm birth may present a risk factor for both ADHD and additional impairments.

Investigation of the effects of risk and protective factors during adolescence is vital, since this period is one of rapid developmental change during which ADHD symptoms can diminish in severity (Willcutt, 2012). Moreover, individuals with high levels of ADHD symptoms are at increased risk of continuing problems related to ADHD during adolescence (Biederman et al., 2011; Rasmussen & Gillberg, 2000). Chapter 5 demonstrated that, during adolescence, IQ and ADHD symptoms significantly predicted each other over time. These findings suggest that ADHD symptoms affect IQ scores, conceivably because ADHD symptoms may interfere with opportunities to benefit from education and other ways to enhance general cognitive ability. In addition, these findings indicate that low IQ may be a risk factor for the persistence of ADHD symptoms over time. This idea is supported by previous research, which demonstrated that higher IQ predicts improved long-term cognitive and functional outcome (Brocki, Nyberg, Thorell, & Bohlin, 2007; Molina et al., 2009), as well as remittance from ADHD in adolescence (Cheung et al., 2015b). While future studies are needed to confirm our findings, these results emphasise the importance of early identification and intervention for

adolescents with ADHD who have lower general cognitive ability, as they are most at risk of adverse long-term outcome.

An environmental factor that might influence the developmental trajectory or course of ADHD during adolescence and adulthood is physical activity. Our recent review, which indicated that exercise has the potential to act as a protective factor for ADHD symptoms and associated impairments (Rommel et al., 2013, see Appendix 1), received support from the analysis in chapter 6. Chapter 6 examined the effect of PA during late adolescence on ADHD symptoms in early adulthood in a population-based sample of MZ twins. In line with a causal hypothesis, PA showed an inverse association with ADHD symptoms, even after genetic and shared environmental factors, as well as baseline ADHD symptoms and BMI, were adjusted for. These findings raise the possibility that lifestyle factors have the potential to impact the trajectory of ADHD symptoms and to lower rates of ADHD persistence from adolescence to adulthood.

It is conceivable that PA and other risk or protective factors impact on the ADHD trajectories via epigenetic processes (Cortessis et al., 2012), which developmentally regulate gene expression independently of the DNA sequence via modifications to DNA, histone proteins and chromatin (Henikoff & Matzke, 1997) and which may set off a cascade of processes that could ultimately link to changes in brain function.

### ***7.3.2 Overlap between ADHD and associated traits and disorders***

By investigating ADHD within a developmental framework, one important aspect to consider is ADHD in adulthood and how adult ADHD may overlap with or differentiate from other adulthood disorders. While diagnostic manuals such as the DSM (American Psychiatric Association, 2013) describe clinical diagnoses in a categorical system based on behavioural symptoms, studies have established considerable evidence for pathophysiological within-disorder heterogeneity (Burdick et al., 2015; Sjöwall et al., 2013), as well as pathogenic overlap between disorders (Lee et al., 2013; Michelini et al., 2015); Skirrow et al., 2014, 2012). Consequently, diagnostic boundaries based on behavioural

symptoms do not seem to correspond seamlessly to findings from neuropsychological and genetic studies, and have been only moderately successful at predicting treatment outcome (Ostacher et al., 2015; Retz & Retz-Junginger, 2014).

The results in chapter 2 provide evidence for commonalities in brain dysfunction between ADHD and BD, with frontal theta power potentially playing a role as a marker of shared neurobiological processes in both disorders. In light of shared cognitive impairments and the overlapping symptomatology of ADHD and BD, these findings represent a move towards uncovering biological markers underlying the pathophysiology shared between the disorders. As highlighted by chapter 2, as well as chapters 3 and 4, EEG and ERP studies can help to elucidate impairments in specific components of neurocognitive systems. While initially based on categorical definitions of disorder, these approaches may further our understanding of the relationship between behaviour and cognitive-neurophysiological abnormalities and provide insight into within-disorder heterogeneity as well as the commonalities and characteristic differences between disorders. By identifying syndromes and impairment based on pathophysiology, it may eventually be possible to move beyond diagnostic boundaries (Insel et al., 2010). This could lead to more objective and precise approaches to diagnosis and prognosis and may eventually result in improved interventions and long-term outcome (Casey et al., 2014).

### **7.3.3 Age effects**

Differences in sample ages may have contributed to the rest-to-task transition effect discrepancies between the QEEG findings in the adult samples in chapter 2 and previous work (Skirrow et al., 2015) and the QEEG findings in the adolescent samples in chapter 3. While chapter 2 and previous research on adults showed a lack of change in slow EEG spectral power (theta) from resting-state to cognitive task condition in the ADHD group (Skirrow *et al.* 2015, chapter 2), in chapter 3 a significant increase in delta power from EO to CPT-OX was found in the ADHD group. The idea that this discrepancy can be attributed to age effects is supported by the negative moderate-to-large relationship of age with EEG spectral power in the delta band in chapter 3.

Moreover, in chapters 3 and 4, even when statistically controlling for age, different patterns of findings emerged for the full sample, which was not matched on age, compared the age-matched subsample, further indicating age effects. Age has previously been shown to impact EEG spectral power in other studies of ADHD (Buyck & Wiersema, 2014; Liechti et al., 2013; Monastra et al., 2001). Research indicates the possibility that developmental trajectories of EEG spectral power in individuals with ADHD may not be linear throughout the lifespan but may deviate in late childhood (Liechti et al., 2013) or adulthood (Poil et al., 2014). While one study demonstrated increased theta power during EO in adolescents with ADHD (mean age=12.81, SD=1.54), but not in children (mean age=9.47, SD=0.84) or adults with ADHD (mean age=42.7, SD=4.4) (Liechti et al., 2013), another study found an atypical developmental trajectory only in adults with ADHD (Poil et al., 2014). Age effects may, therefore, also explain the inconsistency in the ADHD EEG literature more generally. They further highlight that the use of increased theta:beta ratio as a marker of ADHD diagnosis (Snyder & Hall, 2006) is not only controversial but fraught with problems of stability and reliability (Arns et al., 2013; Jeste et al., 2015). Future research must be aware of age effects and the heterogeneity introduced by wide age ranges, particularly in adolescent samples. Longitudinal studies are needed to fully elucidate the maturational effects on ADHD and associated impairments.

## **7.4 Limitations**

### ***7.4.1 Effects of medication***

Potential effects of medication are a typical challenge associated with psychiatric cross-disorder research. In chapters 2, 3 and 4, individuals with ADHD refrained from taking stimulant medication for 48 hours prior to the testing session. Consequently, the results of these studies cannot be attributed to any short-term effects of stimulant medication. Yet, long-term effects of medication use cannot be precluded. In chapter 2, individuals in the BD group and some individuals in the ADHD group were taking non-stimulant medication. For ethical reasons due to the potential risk of adverse effects from

discontinuation of treatment, participants were not asked to stop taking mood stabilisers, anti-psychotic medication or anti-depressants, which they had been prescribed. Although the understanding of the effects of medications on QEEG is still limited, no significant differences between medicated and unmedicated individuals with euthymic BD on QEEG have been found (Degabriele & Lagopoulos, 2009). It is, therefore, unlikely that the results in this study are a result of medication effects. However, medication cannot be excluded as a potential confounder factor and studies of non-medicated individuals are needed to elucidate the effects of medication on EEG power.

### ***7.4.2 Generalisability***

The age ranges of the samples included in this thesis were restricted to adolescence (chapters 3, 4, 5 and 6) or adulthood (chapters 2 and 6). It is, therefore, unclear whether results from this thesis can be generalised to earlier or later stages in development. Maturational effects on EEG and ERP measures are well documented (Buyck & Wiersema, 2014; Clarke et al., 2001; Gasser, Verleger, et al., 1988; John et al., 1980; Doehnert et al., 2010, 2013; Fallgatter et al., 1999; Liechti et al., 2013; Matoušek & Petersén, 1973; Somsen et al., 1997; Zurrón et al., 2014). Furthermore, estimates of genetic and environmental effects, as in chapter 5, are always based on a specific population at a specific point in time (Plomin, DeFries, McClearn, & McGuffin, 2008). To understand the neurophysiological impairments of ADHD and associated disorders, as well as the aetiological relationship between ADHD and risk and protective factors across the lifespan, replication of these investigations at different developmental stages is required. Longitudinal studies may contribute further to the understanding of stability and change in these impairments and associations.

In addition, preterm (Kerr-Wilson et al., 2012) and control participants included in the analyses in chapters 2, 3 and 4 exhibited above average IQ and may, therefore, not be fully representative of more typical preterm and control samples. Whether the findings based on these groups generalise to more typical preterm-born individuals and typically-developing controls remains to be tested in future studies of individuals with more characteristic IQ profiles.

Moreover, the investigation in chapter 2 was conducted in a homogenous all-female sample. Research in all-female ADHD samples is still limited because of the higher rates of ADHD symptoms and diagnoses consistently reported for boys (Willcutt, 2012). Yet, the increased representation of females and the approximately equal distribution of males and females in adults with ADHD (Biederman et al., 1994; Biederman et al., 2004; Rucklidge, 2010) necessitate this research. Although gender differences were not tested directly, the results replicate previous work in an all-male sample (Skirrow et al., 2015), rendering gender effects unlikely.

Chapters 5 and 6 used population-based samples of twins to investigate the risk or protection factors IQ and PA. Consequently, the results may not generalise to clinical samples. The associations of ADHD symptoms with verbal and performance IQ, for instance, have been found to be greater (Frazier et al., 2004; Rommelse et al., 2008) and may, therefore, differentiate in individuals diagnosed with ADHD. Yet, examining large unselected general population samples decreases the risk of possible selection biases associated with clinical samples. In addition, previous studies have demonstrated that the clinical disorder represents the extreme of a trait that varies continuously throughout the population rather than being qualitatively different (Frazier et al., 2007; Haslam et al., 2006; Larsson et al., 2012; Lubke et al., 2009), suggesting that the results may extend to clinical populations. Nevertheless, future research will have to examine how clinical impairment, the diagnostic requirement in addition to ADHD symptoms, influences the pattern of results.

### ***7.4.3 Rater effects***

In chapters 3 to 6 of this thesis, ADHD symptom ratings were based on parent-report. Whereas multiple-informant accounts are the gold standard for a systematic evaluation of ADHD symptoms and to establish the pervasiveness of these symptoms across settings (American Psychiatric Association, 2013; Taylor et al., 2004; World Health Organization, 1992), parent-rated ADHD symptoms demonstrate the highest and most consistent heritability estimates compared to self- and teacher-ratings (Nikolas & Burt, 2010). Moreover, the



predictive validity of parent-report with regards to long-term outcome is more accurate than that of self-report in child and adolescent samples (Barkley et al., 2002).

The use of self-report to measure PA in chapter 6 may also be considered a limitation (Paulhus & Vazire, 2007), because due to difficulties with time estimation, executive function (EF) and working memory, individuals with high levels of ADHD symptoms might report less accurately on PA. Yet, in our unselected population-based twin sample this issue is likely to be less pronounced. In addition, the use of cross-informant data (i.e. parent-report for ADHD symptoms and self-report for PA) can be seen as a strength.

## **7.5 Future directions**

### ***7.5.1 Replication***

The research conducted for this thesis, especially in chapters 2, 3 and 4, was the first of its kind and requires replication in large, independent samples before firm conclusions can be drawn. Future studies should include samples at different developmental stages to understand the change and stability of cognitive-neurophysiological abnormalities in individuals with ADHD and BD across the lifespan. Findings from these studies may inform the research on maturational effects on EEG and ERP measures as well as age-related decline. In addition, longitudinal investigations may elucidate these issues further. Longitudinal studies may also further our understanding of the discrepancy in QEEG findings between individuals with adult ADHD and adolescents with ADHD in chapters 2 and 3. In addition, ADHD and BD symptoms as well as gestational age lie along a continuum and should be explored as continuous variables, for example by investigating whether a dose effect in the degree of prematurity exists in relation to ADHD-like symptoms or ADHD diagnosis.

### ***7.5.2 Advanced EEG analysis approaches***

High variability in performance measures and cognitive-neurophysiological responses has been demonstrated in ADHD (Castellanos et al., 2005; Frazier-Wood et al., 2012; Kuntsi & Klein, 2012; Uebel et al., 2010). Yet, most EEG and

ERP analyses involve the enhancement of the signal-to-noise ratio by means of averaging data, at the expense of trial-by-trial variations for the individual. As a result, the underlying intra-individual variability in cognitive-neurophysiological responses in ADHD is not fully reflected in EEG and ERP findings.

Approaches such as time-frequency analysis and individual-level ICA have the potential to directly explore the degree of intra-individual variability in EEG or ERP responses on a trial-by-trial basis, enabling the investigation of lapses of attention thought to underlie RTV (Kuntsi & Klein, 2012). The use of these state-of-the-art techniques may further increase the low signal-to-noise ratio in cognitive-neurophysiological data and afford finer resolution. Lastly, time-frequency analysis and individual-level ICA may help to elucidate the significance of EEG spectral power by allowing for the exploration of the various cognitive processes underlying task performance (Lenartowicz et al., 2014; McLoughlin, Makeig, et al., 2014; McLoughlin, Palmer, et al., 2014). This last point may be particularly important to understand findings such as the increased delta (chapter 3) power in individuals with ADHD during cognitive task performance, which could reflect compensatory mechanisms (Lenartowicz et al., 2014).

### ***7.5.3 Sibling model fitting***

Another future direction, using the preterm and control sibling pairs, is structural equation model-fitting to explore the extent to which the covariance between the cognitive-neurophysiological variables and ADHD symptoms can be explained by familial or non-shared influences. We further plan to investigate the degree to which a separation between a non-shared insult pathway to cognitive-neurophysiological impairments is observed among the preterm-born adolescents and a familial pathway is observed among the adolescents with ADHD. As well as looking at preterm birth as a categorical condition, we will conduct the analyses using continuous proxies of preterm birth, namely gestational age and birth weight.

#### ***7.5.4 Investigation of the effects of physical activity in ADHD***

Better-quality evidence is required to firmly establish the nature and extent of positive effects of PA on individuals with ADHD. Both acute and chronic effects of PA on ADHD need to be investigated in large, adequately powered, blind sham-controlled randomised clinical trials. In addition, follow-up studies are needed to establish whether any short-term effects are followed by longer-term benefits of both acute and chronic PA. As PA can elicit gene expression changes mediated by alterations in DNA methylation (Barrès et al., 2012; Nitert et al., 2012; Rönn et al., 2013; Voisin, Eynon, Yan, & Bishop, 2014), the possibility emerges that some of the positive effects of PA could be caused by epigenetic mechanisms. Consequently, we aim to investigate the effects of acute exercise and habitual physical activity on cognition and brain function, as well as the potential underlying molecular mechanisms, in our sample of young adults with childhood ADHD and the population-based controls as well as their siblings (the ADHD and control sibling pairs used in chapters 3 and 4). We plan to investigate whether individuals with higher levels of current habitual PA and aerobic fitness show greater improvement on the cognitive-neurophysiological test battery and ADHD symptoms over time. Moreover, we will test whether the effects of PA and fitness on cognitive-neurophysiological performance and ADHD symptoms remain after controlling for familial factors. Lastly, in a randomised controlled trial we plan to explore whether acute exercise induces cognitive-neurophysiological, epigenetic, cortisol and skin conductance changes. Future prospective longitudinal studies are also needed to establish whether any short-term effects are followed by longer-term benefits. In the future, the intensity, frequency, and duration of PA required to yield benefits for individuals with ADHD will need to be established. Studies will need to affirm whether and to what extent factors such as age, fitness levels, or ADHD symptom severity affect who is likely to respond to a PA-based intervention.

#### **7.6 Overall conclusions**

In summary, this thesis employed a combination of cognitive-neurophysiological as well as genetically-sensitive longitudinal designs to study the relationship of ADHD with bipolar disorder and preterm birth, as well as the risk or protective

factors of IQ and physical activity. The findings suggest commonalities in brain dysfunction between ADHD and BD, with frontal theta power potentially playing a role as a marker of shared neurobiological processes in both disorders. Term-born individuals with ADHD and individuals born preterm demonstrated both differences and similarities in brain function. While we found deviating abnormalities in EEG spectral power between ADHD and preterm birth, differences as well as similarities in ERP components emerged, pointing to more wide-ranging impairments in preterm birth. The results from this thesis further suggest that ADHD symptoms may put adolescents at risk for decreased IQ scores, and vice versa. These findings highlight the need for early identification and intervention for those adolescents with ADHD who have lower general cognitive ability, to reduce ADHD symptoms and the risk for lower IQ and associated long-term consequences. PA, on the other hand, may represent a protective factor for ADHD and a novel treatment target, showing an inverse association with total ADHD, hyperactivity-impulsivity and inattention symptoms, even after adjusting for unmeasured confounding factors, as well as ADHD symptom levels and BMI at baseline. Overall, by using a combination of cognitive-neurophysiological and genetically-sensitive longitudinal designs, we demonstrated certain commonalities in brain dysfunction between ADHD and BD. Whereas preterm birth and lower IQ present risk factors for ADHD, physical activity emerges as a potential protective factor.

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## **Appendix 1. Publication: Protection From Genetic Diathesis in Attention-Deficit/Hyperactivity Disorder: Possible Complementary Roles of Exercise.**

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# Protection From Genetic Diathesis in Attention-Deficit/Hyperactivity Disorder: Possible Complementary Roles of Exercise

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**Objective:** The degree of functional impairment and adverse developmental outcomes in individuals with attention-deficit/hyperactivity disorder (ADHD) likely reflect interplay between genes and environment. To establish whether physical exercise might reduce the level of ADHD symptoms or ADHD-related impairments, we conducted a comprehensive review of the effect of exercise in children with ADHD. Findings on the impact of exercise in animals and typically developing human beings, and an overview of putative mechanisms involved, are also presented to provide the context in which to understand this review. **Method:** The electronic databases PubMed, OVID, and Web of Knowledge were searched for all studies investigating the effect of exercise in children and adolescents with ADHD, as well as animal models of ADHD behaviors (available in January 2013). Of 2,150 initially identified records, 16 were included. **Results:** Animal studies indicate that exercise, especially early in development, may be beneficial for ADHD symptom reduction. The limited research investigating the effect of exercise in children and adolescents with ADHD suggests that exercise may improve executive functioning and behavioral symptoms associated with ADHD. Although animal research suggests that brain-derived neurotrophic factor (BDNF) and catecholamines (CAs) play a role in mediating these effects, the association between BDNF and ADHD remains unclear in human beings. **Conclusions:** The potential protective qualities of exercise with regard to reducing symptoms and impairments commonly associated with ADHD may hold promise for the future. Further research is needed to firmly establish whether there are clinically significant effects of exercise on the severity of ADHD symptoms, impairments, and associated developmental outcomes. *J. Am. Acad. Child Adolesc. Psychiatry*, 2013;52(9):900–910. **Key Words:** attention-deficit/hyperactivity disorder (ADHD), epigenetics, exercise, physical activity, protective factors

Attention-deficit/hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder characterized by developmentally inappropriate and impairing levels of hyperactivity, impulsivity, and/or inattention.<sup>1</sup> ADHD is associated with multiple cognitive impairments, including lower average IQ,<sup>2</sup> impairment in attentional processing, response inhibition, and other aspects of executive functioning,<sup>3</sup> which share genetic/familial risks with ADHD.<sup>3,4</sup> Genetic factors play a pivotal role in the susceptibility to ADHD, with 60%

to 75% or more of the variance in ADHD symptoms attributable to genetic variation.<sup>5,6</sup> Environmental factors are also likely to contribute to the development of the disorder and to the associated emotional, behavioral, and academic difficulties.<sup>7</sup> Moreover, the effects of genetic risks on development may depend on exposure to either adverse or enriched environments, leading to either negative or positive long-term outcomes.<sup>8,9</sup> Such gene–environment interactions mean that specific environments may be more or less beneficial to the long-term outcomes in children with ADHD.

Several environmental risk factors have been linked to ADHD.<sup>7</sup> Yet, less attention has been paid to protective factors that might reduce levels of ADHD symptoms and impairments associated



This article is discussed in an editorial by Dr. Samuele Cortese on page 894.

with the disorder. We define protective factors as influences that increase adaptive functioning following environmental adversity or genetic risk. Here, we investigate exercise as a factor that may diminish an individual's level of ADHD symptoms or the impairments associated with the disorder by modifying the effects of genetic and environmental risks on developmental outcomes. We examine exercise as a factor that may diminish an individual's likelihood of developing ADHD or the impairments associated with the disorder. The idea that exercise may have protective qualities for individuals with ADHD gains support from animal research examining the impact of exercise on neural functioning, brain growth, and development, as well as from human studies indicating that exercise positively affects executive functioning and inhibitory control in adults and in typically developing children. Preliminary research has also been carried out to explore the utility of exercise as a protective factor or alternative treatment strategy in ADHD. Before providing a comprehensive review of the role of exercise in ADHD, we will provide the context in which to understand this review by presenting research findings on the impact of exercise on cognition in animals and in typically developing human beings, and an overview of the putative mechanisms involved.

## NEUROBIOLOGY OF ADHD

The precise neurobiological mechanisms underlying ADHD are poorly understood. Their complexity is likely due to the interplay of various structural, functional, and developmental brain alterations in individuals with ADHD, such as abnormalities in the white matter fibers that connect gray matter regions, hypoactivity of frontal regions, and aberrant or delayed brain development.<sup>10</sup> Dysregulation of dopaminergic and noradrenergic neurotransmission has also been widely implicated in the pathophysiology of ADHD.<sup>11</sup> The catecholaminergic system has been the key target for pharmacotherapy in ADHD.<sup>12</sup> In molecular genetic studies of ADHD, 1 of the most robust findings to date is the association with the 7-repeat allele of the dopamine D4 receptor gene,<sup>13</sup> and catecholamines (CA) are known to play a pivotal role in the regulation of psychomotor activity, motivation, inhibition, and attention,<sup>14</sup> all of which are compromised in ADHD.<sup>12</sup> (For comprehensive reviews of the neurobiology and genetics of ADHD, see Cortese<sup>10</sup> and Faraone *et al.*<sup>15</sup>)

One recent theory has focused on BDNF as a factor that has an impact on the dopaminergic function underlying aspects of ADHD.<sup>14,16–19</sup> The idea that BDNF interacts with the dopaminergic dysfunctions seen in individuals with ADHD was initially suggested by research showing that stimulant medications increase the expression of BDNF in the rat brain,<sup>19</sup> in addition to studies suggesting that there is an association between genetic variants in BDNF and risk for ADHD. In a community-based cohort of 1,236 Swedish individuals assessed at ages 8 to 9, 13 to 14, and 16 to 17 years, the presence of the Val<sup>66</sup>Met polymorphism in BDNF gene was associated with increased hyperactive-impulsive ADHD symptom counts at ages 8 to 9 and 13 to 14 years.<sup>19</sup>

However, the overall evidence for the genetic association of BDNF with ADHD is far from clear. A recent meta-analysis of published and unpublished data from 4 different centers (conducted as part of the International Multicentre Persistent ADHD CollaboraTion [IMpACT]) investigated the association of ADHD with the most frequently reported BDNF polymorphism, Val<sup>66</sup>Met, in a total sample of 1,455 ADHD adults and 2,247 sex-matched controls.<sup>20</sup> The investigation of these 4 populations yielded no significant association between BDNF genotype and ADHD. Like several studies before,<sup>21–23</sup> the investigation of these 4 populations yielded no significant association between BDNF and ADHD, highlighting the known difficulties in replicating candidate gene association studies; potentially related to heterogeneity of the genetic effects across development or related to different clinical subgroups.

The conception of exercise as a potential protective factor for ADHD is suggested by animal literature investigating the positive impacts of physical activity on neurobiological mechanisms implicated in ADHD. In healthy rodents, exercise has been found to augment several factors often compromised in ADHD: neural plasticity,<sup>24</sup> cerebral blood flow,<sup>25</sup> levels of synaptic protein,<sup>26</sup> and extracellular dopamine and norepinephrine levels in the central nervous system.<sup>27</sup> Furthermore, physical exercise has been shown to lead to an increase in rodent serum and brain levels of BDNF, which is part of vital neurodevelopmental processes central to the survival and differentiation of noradrenergic<sup>28</sup> and dopaminergic<sup>29</sup> neurons.<sup>30–34</sup> This upregulation of BDNF is one potential mechanism by which exercise induces its positive effects. BDNF levels in the hippocampus

have been directly linked to the enhanced memory and learning processes that are observed with exercise treatments in rodents.<sup>35</sup> One process expected to mediate the upregulation of BDNF involves epigenetic influences on gene expression. Epigenetic processes, which developmentally regulate gene expression independently of the DNA sequence via modifications to DNA, histone proteins, and chromatin,<sup>36</sup> have been shown to be sensitive to a range of environmental influences.<sup>37</sup> Indeed, both acute<sup>38</sup> and chronic<sup>39</sup> exercise have recently been found to elicit gene expression changes linked to changes in DNA methylation. However, the strength of the association between BDNF and ADHD in human beings and its potential role in eliciting the established positive effects of exercise on cognition and psychological health<sup>40</sup> remain unclear.

## COGNITIVE EFFECTS OF EXERCISE IN HUMAN BEINGS

Beyond the animal literature, an emerging body of evidence highlights the benefits of exercise for human beings.<sup>40</sup> Research on the effect of exercise in human beings has found, for example, that older adults who were more aerobically fit or who took part in exercise programs demonstrated greater task-related activity in areas of the brain implicated in ADHD; namely, regions of the prefrontal and parietal cortices, with the largest fitness-induced benefits occurring for executive functions.<sup>41</sup> Furthermore, there is evidence that, in human beings, exercise facilitates catecholaminergic neurotransmission,<sup>42,43</sup> augments serum BDNF levels,<sup>31,34</sup> enhances cognitive performance, and affects cerebral structures positively by increasing cortical tissue density and brain volume.<sup>41,44</sup> A meta-analysis of 44 studies, which investigated the effects of both acute and chronic exercise on cognition in children, yielded an overall effect size (ES) of 0.32. Despite the ES being only moderate, these findings indicate a significant positive effect of exercise on cognitive performance. As the ES of exercise was greater in the children who were classified as “mentally impaired” (0.42), this moderate overall ES may point to greater beneficial effects of exercise in children with developmental disorders.<sup>45</sup> Other, more recent reviews of the effects of exercise on neurotypical children’s intelligence, cognition, and academic achievement confirmed the positive effect of exercise, especially on executive functioning (EF),<sup>40,46,47</sup> a cognitive domain often

impaired in individuals with ADHD.<sup>48</sup> Chronic and acute exercise was reported to improve inhibitory control, whereas the effects on attention, perception, and visuo-motor coordination were more limited.

## ROLE OF EXERCISE IN ADHD

Animal and neurotypical human studies provide support for the notion that exercise enhances brain structure, cognitive performance, and neural functioning. As enhanced neural functioning has been suggested to be associated with a remission of ADHD symptoms,<sup>49,50</sup> exercise may hold promise for preventing the emergence of ADHD during childhood and as an early intervention in children presenting with high levels of ADHD symptoms, potentially inducing lasting changes in ADHD symptom severity. Our aim here, therefore, is to offer a review of the literature investigating the effect of exercise in ADHD, including cognitive impairments as well as ADHD symptoms, and to provide a rationale for further research in this area.

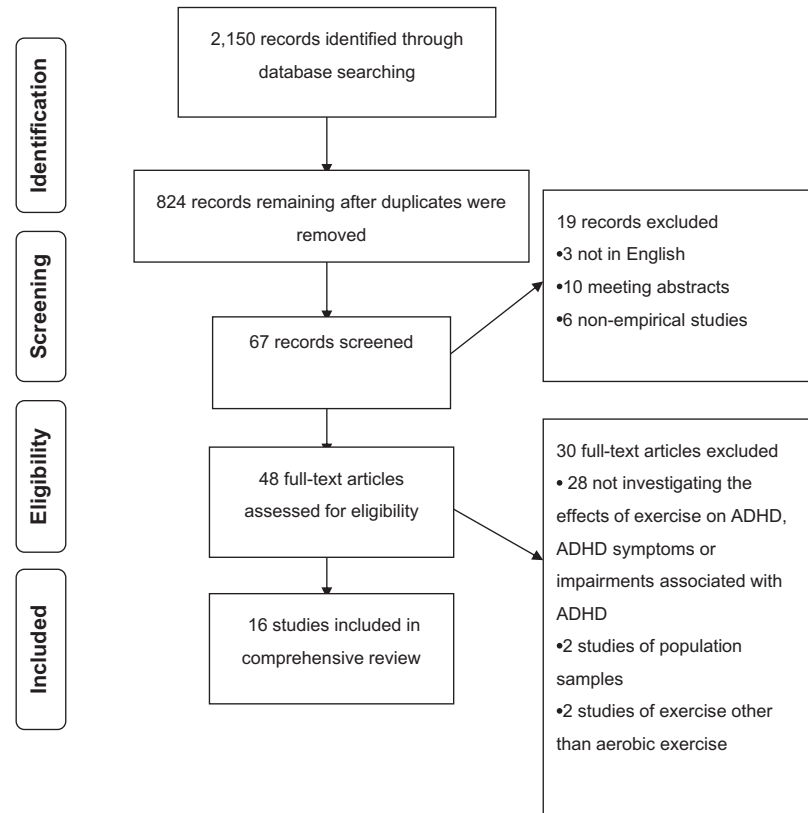
## SELECTION CRITERIA

A comprehensive review was conducted to ensure a thorough search of the literature. The electronic databases PubMed, OVID and Web of Knowledge were searched. Key words searched included *attention deficit hyperactivity disorder*, *ADHD*, *attention deficit disorder*, *ADD*, and *hyperkinetic syndrome* with either *sport\**, *exercise*, or *physical activity*. The inclusion criteria for studies reviewed here were as follows: the paper was written in English; published in an internationally peer-reviewed journal before January 2013; participants were children and/or adolescents diagnosed with ADHD or animal models of ADHD behaviors; (d) an empirical study (including correlational, observational and longitudinal designs) of aerobic exercise. Using these search terms and inclusion criteria, 2,150 records were identified. After screening these records for eligibility as shown in Figure 1<sup>51</sup>, 16 studies were included in the comprehensive review. An overview of these studies can be found in Table 1.<sup>52–67</sup>

## EFFECTS OF EXERCISE IN ANIMAL MODELS OF ADHD BEHAVIORS

The impact of voluntary exercise on attentional functioning in spontaneously hypertensive rats (SHR), an animal model of ADHD behaviors, has been investigated in 3 studies by the same

**FIGURE 1** Flow diagram depicting the number of records identified, included and excluded in the comprehensive review, and the reasons for exclusions. Source: Moher *et al.* (2009).<sup>51</sup> ADHD = attention-deficit/hyperactivity disorder.



research group. The first and second study explored exercise effects in adult<sup>52</sup> and adolescent<sup>54</sup> SHRs, respectively. The third study compared the effects of exercise on adult SHRs to the effects of the stimulant drugs methylphenidate (MPH) and atomoxetine (ATMX).<sup>55</sup> In all studies, the rats in the exercise groups had free access to a shared running wheel for a few weeks before and throughout the study. The exercise group was compared to other SHRs with no access to a running wheel (nonexercising SHRs). Wistar-Kyoto rats (WKY) were used as an animal model of neurotypical behaviors, as they are the most appropriate controls for rat models of ADHD behaviors.<sup>68</sup> During the orienting procedure, all rats received repeated presentations of a visual stimulus (light). Hopkins *et al.*<sup>52</sup> showed that nonexercising adult SHRs demonstrated more unconditioned orienting behavior, as indicated by rearing up on the hind legs, than WKY. Exercise reduced orienting in female but not male adult SHRs.

Exercising adolescent SHRs, similar to exercising female adult SHRs, exhibited levels of

unconditioned orienting behavior resembling that in WKY.<sup>54</sup> Nonexercising adolescent SHRs showed higher levels of unconditioned orienting behavior. The authors propose that this indicates their difficulty in ignoring irrelevant stimuli. Treatment with MPH (0.125 mg/kg), ATMX (0.125 mg/kg), or exercise also reduced orienting behavior in female adult SHRs to the level observed in WKY rats, with exercise just as effective as MPH or ATMX. Taken together, these findings suggest that exercise has a greater effect in females and earlier on in development. Unfortunately, ES could not be established from the data available. These findings should be confirmed using quantifiable measures of exercise and a standardized measure of attention, such as a multiple-choice serial reaction time test.

The effects of involuntary exercise and MPH on activity levels and spatial learning memory in relation to dopamine synthesis and BDNF expression have also been explored in SHRs.<sup>53</sup> Rats in the MPH group received 1 mg/kg MPH orally once a day for 28 days, whereas rats in the exercise group were made to run on a treadmill

**TABLE 1** Overview of All Studies on Exercise and Attention-Deficit/Hyperactivity Disorder (ADHD) Included in the Comprehensive Review

Reference	Design	Intervention/Measure of Physical Activity	Sample Size (Males: Females)	Mean Age (SD) in Years Unless Stated	Cohen's d
Hopkins <i>et al.</i> (2009) <sup>52</sup>	Case-control (3 groups)	SHR exercise group: 24-hour access to running wheel, 2 weeks before and throughout study SHR no-exercise group: no intervention WKY group: no intervention	69 SHRs (37:32), 29 WKYs (14:15)	8 weeks	Orienting behavior; data not available
Kim <i>et al.</i> (2011) <sup>53</sup>	Case-control	SHR exercise group: low-intensity treadmill running 30 minutes per day, 5 times per week, for 28 days SHR MPH-treated group: 1 mg/kg MPH orally per day for 28 days SHR exercise and MPH-treated group SHR controls Controls	60 (60:0)	N/A "adult"	Decrease in open field activity: 2.85
Robinson <i>et al.</i> (2011) <sup>54</sup>	Case-control	SHR exercise group: 24-hour access to running wheel, 3 weeks before and throughout study SHR non-exercise group: no intervention WKY controls: no intervention	32 SHRs (16:16), 16 WKYs (8:8)	28–32 days	Orienting behavior; data not available
Robinson <i>et al.</i> (2012) <sup>55</sup>	Case-control	SHR exercise group: 24-hour access to running wheel, 3 weeks before and throughout study; saline injection SHR controls: saline-injection SHR MPH-treated group: 1.0 ml/kg 10 minutes before behavioral task SHR atomoxetine-treated group: 1.0 ml/kg 30 minutes before behavioral task WKY controls WKY exercise group WKY MPH-treated group WKY atomoxetine-treated group	74 SHRs (0:74), 32 WKYs (0:32)	8–9 weeks	Orienting behavior; data N/A
Ahmed and Mohamed (2011) <sup>56</sup>	Case-control, randomly assigned	Exercise group: 3 sessions/week for 10 weeks (aerobic exercise) Controls: no intervention	84 (54:30)	13.9 (1.6)	Attention: 0.50 Motor skills: 0.59 Academic and classroom behavior: 1.1
Chang <i>et al.</i> (2012) <sup>57</sup>	Case-control, randomly assigned	Exercise group: acute moderate-intensity exercise (30 minutes) Controls: watched exercise-related video (30 minutes)	40 (37:3)	10.4 (0.9)	Color–Word Stroop: 0.57 Total WCST: 0.31

TABLE 1 Continued

Reference	Design	Intervention/Measure of Physical Activity	Sample Size (Males: Females)	Mean Age (SD) in Years Unless Stated	Cohen's d
Gapin <i>et al.</i> (2010) <sup>58</sup>	Within-group comparison	Daily step counts and minutes per day spent in moderate-to-vigorous intensity exercise over 7 days	18 (18:0)	10.6 (1.5)	Tower of London task: 0.57
Kang <i>et al.</i> (2011) <sup>59</sup>	Case-control	Exercise group: medication and sports therapy (twelve 90-minute sessions over 6 weeks) Controls: medication and behavior control education	28 (28:0)	8.5 (1.2)	Attention ratings: 0.32 EF: 0.37 Cooperativeness: 0.54
Kiluk <i>et al.</i> (2009) <sup>60</sup>	Within-group comparison	CBCL indicating number of sport activities	65 (40:25)	Range: 6–14	Boys: 1.52 Girls: 1.23
Lufi and Parish-Plass (2013) <sup>61</sup>	Clinical comparison	Twenty 90-minute sessions (including discussions, individual sports activity, team games)	32 (32:0)	10.9 (1.6)	Total CBCL: 0.45
McKune <i>et al.</i> (2003) <sup>62</sup>	Case-control, allocation to groups	Exercise group: five 1-hour sessions per week for 5 weeks Controls: no intervention	19 (13:6)	11 (1.9)	CRS-Parent; data N/A
Medina <i>et al.</i> (2010) <sup>63</sup>	Between-group (MPH users vs. non-users) comparison	Aerobic exercise for 30 minutes	25 (25:0)	9.5 (2.9)	Hit RT SD: 0.49
Pontifex <i>et al.</i> (2012) <sup>64</sup>	Case (ADHD)—control (neurotypical) and within-group comparison	Acute 20-minute moderate-intensity aerobic exercise	40 (28:12)	9.6 (0.5)	Response accuracy: 0.94
Tantillo <i>et al.</i> (2002) <sup>65</sup>	Case-control	Two exercise bouts (first maximal intensity, second submaximal intensity), 1 rest condition (silent cartoon); on consecutive days	43 (21:22)	10 (1.6)	Acoustic startle eye-blink response latency: 1.14
Verret <i>et al.</i> (2012) <sup>66</sup>	Case-control	Exercise group: Three 45-minute sessions per week for 10 weeks (moderate-to-vigorous aerobic, muscular, and motor-skills exercise) Controls: no intervention	21 (20:1)	9.1 (1.1)	Attention problems: 1.68 Auditory sustained attention: 0.13
Wigal <i>et al.</i> (2003) <sup>67</sup>	Case-control	Two separate cycle ergometer sessions on different days within 1 week	18 (18:0)	8.5 (0.5)	Catecholamine response; data N/A

Note: CBCL = Child Behavior Checklist; CRS = Conners' Rating Scale; EF = executive function; ES = effect size; SHR = spontaneously hypertensive rat; MPH = methylphenidate; N/A = not available; WCST = Wisconsin Card Sorting Test; WKY = Wistar-Kyoto rat.



for 30 minutes per day 5 times per week for 28 days. Both MPH and exercise alleviated hyperactivity effectively (see Table 1 for ES) and improved spatial learning memory, an effect seemingly mediated by the augmentation of dopamine levels and BDNF expression. These animal studies suggest that exercise could have a positive impact on symptoms of ADHD, especially early in development, potentially mediated by effects on BDNF and CAs.

### EFFECTS OF EXERCISE ON INDIVIDUALS DIAGNOSED WITH ADHD

Although evidence for effects of exercise on symptoms and impairments associated with ADHD is limited, interest in novel treatment approaches is growing. It is, thus, encouraging that both chronic and acute exercise have been linked to improvements in EF in school-aged children with ADHD. One study investigating the effects of acute exercise on EF reported that 30 minutes of moderate-intensity running facilitated performance on the color-word condition of the Stroop task and certain aspects of the Wisconsin Card Sorting Test in 20 children with ADHD who were randomly assigned to the exercise group, relative to 20 children with ADHD assigned to the control condition of watching an exercise-related video.<sup>57</sup> However, it should be noted that exercise did not have an effect on all measures of EF, and that ES were small to moderate. Another study looking at the impact of acute exercise used a within-participant design to assess the effect of a 20-minute, moderate-intensity bout of exercise in 20 children diagnosed with ADHD and 20 healthy matched controls.<sup>64</sup> After exercise, both the ADHD and the control group exhibited greater response accuracy on a version of the Eriksen Flanker Task, measuring inhibitory control, relative to a seated reading condition. Acute exercise, thus, seems to have at least some effect on certain tasks assessing EF. The effect also seems to be universal and not specific to ADHD.

The impact of chronic exercise on EF has been assessed by measuring the amount of moderate- to high-intensity exercise performed by children with ADHD each day over a period of 1 week using an accelerometer.<sup>58</sup> Exercise quantity significantly predicted performance on the Tower of London task, and was positively associated with working memory, inhibition, and information processing in 18 boys with ADHD. Similarly, a

6-week prospective trial of 12 biweekly sessions demonstrated that EF, as measured by the Korean version of the Wechsler Digit symbol substitution test, was significantly improved by exercise relative to behavioral educational sessions in 28 boys with ADHD.<sup>59</sup> Teachers also noted significant improvements in the cooperativeness of boys in the exercise group, compared to boys who received behavioral education. Although no significant changes were found with regard to hyperactivity scores, inattention scores improved in the exercise group.

A study examining the association between attention and chronic exercise in 84 individuals with ADHD used a moderate-intensity, 10-week exercise program of 3 sessions per week, which included upper limb, lower limb, trunk, and neck aerobic exercises, in addition to free running.<sup>60</sup> Individuals were randomly assigned to 2 equal groups: the exercise group and the control group, which did not receive an exercise intervention.<sup>56</sup> In this study, exercise significantly improved teacher ratings of attention, motor skills, and academic and classroom behavior. Correspondingly, another study assessed the effects of a 10-week, moderate- to high-intensity exercise program on fitness, cognitive functions, and ADHD-related behavior in 10 children with ADHD, and compared the effects to a no-intervention control group consisting of 11 children with ADHD. This study reported significant improvements in muscular capacities, motor skills, level of information processing, and parent- and teacher-rated social, thought and attention problems after the intervention.<sup>66</sup> The effect of chronic exercise on behavior ratings was further investigated in a nonrandomized, 5-week exercise program in 19 children with ADHD.<sup>62</sup> Although no significant group differences were found between the exercise and no-exercise control group with regard to changes in parent-rated Conners' Rating Scale (CRS) scores, total behavior, attention, emotional, and motor skills were rated as having improved for both groups after the intervention. These findings suggest nonspecific treatment effects, conceivably due to rater expectation, rather than real effects of exercise. This last view is consistent with a recent meta-analysis on nonpharmacological interventions for ADHD, which found that the ES for nonpharmacological interventions depended on the rater's blinding status.<sup>69</sup> Although some studies of the effect of chronic exercise on EF used nonblinded ratings

and must be interpreted with caution, others are more convincing because of their use of relatively blinded raters, such as teachers and the objective cognitive tests that were used.

Another study focused on the association of exercise with different aspects of mental health seen in children with ADHD. In a retrospective study, participation in 3 or more sports was reported to be significantly associated with a reduced number of anxiety and depressive symptoms and rates of co-occurring mood disorders in children with ADHD compared to control individuals with learning disabilities.<sup>60</sup> Yet, parent report of the number of sports that a child plays is an arbitrary measure, as children playing 1 sport might be more dedicated to that sport and not necessarily less fit than children participating in more than 1 sport. As association does not imply causation, the correlation between the number of sports played and anxiety and depression symptoms could alternatively reflect that children who are less anxious are more likely to be engaged in a greater number of different sports, or that depressed children have less need for social interaction and, thus, participate in fewer sports. However, a study exploring a sport-based group therapy program in boys with ADHD and boys with other behavioral disorders supported the finding that sports participation (20 sessions 90 minutes each over 1 school year) improves anxiety and other behavioral scores.<sup>61</sup> Yet, the intervention included group discussions as well as exercise, and it remains unclear how large the effect of each aspect of the intervention was on the outcome measure. Furthermore, the lack of a neurotypical control group does not allow for conclusions about specific effects of the intervention.

To elucidate the putative mechanism underlying the effects of exercise, 3 studies have investigated the relationship between CA levels and exercise in individuals with ADHD; yet, findings are inconclusive and contradictory. Among the first to investigate the impact of exercise in individuals with ADHD, Tantillo *et al.*<sup>65</sup> studied the rate of spontaneous eye blinks (SEB), the acoustic startle eye-blink response (ASER), and motor impersistence, as noninvasive measures sensitive to dopamine agonists, in 8- to 12-year-olds with and without ADHD. Although SEB and ASER had previously been used as sensitive measures of dopamine function in children with ADHD,<sup>70,71</sup> no clear link between ASER and ADHD has been established in human beings. Both the ADHD and control group

underwent 2 bouts of exercise and 1 rest condition on consecutive days. The main findings were increased SEB rate, decreased latency of ASER, and improved motor persistence after exercise in boys with ADHD, whereas such improvements were not observed in controls. Although the authors concluded that exercise augments dopamine levels in children with ADHD but not in neurotypical controls, the alternative interpretation is that the physiological effect is consistent across groups but emerges as significant only in those showing pathological levels of ADHD symptoms. In a more direct investigation of CA levels in response to exercise, Wigal *et al.*<sup>67</sup> compared 10 children with combined subtype ADHD, to 8 age- and sex-matched controls on their CA levels after 2 separate cycling ergometer sessions. CA levels were measured by a radioenzymatic technique based on the conversion of the CA to radiolabeled metanephrine and normetanephrine. This CA assay uses an extraction technique that eliminates substances that may inhibit the radioenzymatic assay, and concentrates the CA to provide a more sensitive assay. Although epinephrine and norepinephrine levels rose in both groups after the exercise sessions, the response was less strong in children with ADHD and, in contrast to controls, their dopamine levels did not increase significantly, contrary to the previous study. The most recent study that examined the relationship between high-intensity exercise, CA levels, and sustained attention in 25 children with ADHD demonstrated that exercise significantly improved response time and normalized impulsivity and vigilance measures, independent of CA.<sup>63</sup> Participants, who were divided into stimulant medication users and nonusers, were assessed on Conners' Continuous Performance Test-II (CPT) at diagnosis, after exercise, and after a 1-minute stretching session (control measure). As chronic use of MPH was associated with significant physiological and attentional effects, a comparison of stimulant users and nonusers on CPT performance suggested that the improvements in cognition seen after exercise were not CA dependent; however, CA levels were not measured directly, and no straightforward conclusion can be drawn from these findings. Furthermore, practice effects may be expected, because the CPT was repeated after only a 1-minute stretching session. Although these findings must be approached with caution because of these and other crucial study design limitations outlined below, the research



investigating the effect of exercise on ADHD provides preliminary evidence of the potential for exercise to reduce emotional, behavioral, and neuropsychological problems seen in children with ADHD.

Overall, based on the limited body of research conducted to date, we can conclude that exercise emerges as a potentially promising intervention for improving EF and behavioral symptoms associated with ADHD. Yet, many of the findings remain inconclusive and warrant further investigation. ES varied from small for auditory sustained attention<sup>66</sup> to large for response accuracy<sup>64</sup> (Table 1). Conflicting findings have also been presented for the putative mechanism involved. This may be explained by several limitations. Concluding causality from non-randomized, retrospective, and cross-sectional data is problematic. Not all of the studies reviewed here are case-control studies, and those that do look at case-control differences are limited by small sample sizes and inadequate control conditions. The nonblinded status of the researchers and scorers may further inflate the positive effects of exercise on the various outcome variables due to the nonspecific effects evoked by a child's participation in a treatment programme. Finally, the heterogeneous nature of and various treatment approaches to ADHD are seldom taken into account, complicating the interpretation and generalizability of the results.

ADHD is best considered in a developmental framework. One neurodevelopmental model of ADHD views the disorder as resulting from early aberrations in brain development that remain relatively static throughout an individual's life time<sup>72</sup>; however, the plasticity of the brain and its interconnected neural circuits allow for recovery from ADHD symptoms and associated impairments over the course of development. Thus, experience-dependent neurodevelopmental processes, such as synaptic pruning or myelination, if facilitated early in childhood, could be used to aid the recovery from ADHD symptoms or to mitigate symptomatic escalation over the course of development. As exercise has been found to enhance neural growth and development and to improve cognitive and behavioral functioning in neurotypical individuals and study animals, we reviewed the literature on the effects of

exercise in children and adolescents with ADHD and animal models of ADHD behaviors.

A limited number of undersized, non-randomized, retrospective, and cross-sectional studies have investigated the impact of exercise on ADHD and the emotional, behavioral, and neuropsychological problems associated with the disorder. The findings from these studies provide some support for the notion that exercise has the potential to act as a protective factor for ADHD. However, better-quality evidence is needed, to firmly establish the nature and extent of positive effects of exercise on children with ADHD. Researchers will need to examine both acute and chronic effects of exercise in large, adequately powered, blind, sham-controlled, randomized clinical trials. In addition, follow-up studies are needed to establish whether any short-term effects are followed by longer term benefits of both acute and chronic exercise. Although it remains unclear which role, if any, BDNF plays in the pathophysiology of ADHD, enhanced neural functioning has been suggested to be associated with the reduction of remission of ADHD symptoms.<sup>49,50,73</sup> As exercise can elicit gene expression changes mediated by alterations in DNA methylation,<sup>38</sup> the possibility emerges that some of the positive effects of exercise could be caused by epigenetic mechanisms, which may set off a cascade of processes instigated by altered gene expression that could ultimately link to a change in brain function.  $\mathcal{E}$

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## **Appendix 2. Baseline corrected ERP analysis for the age-matched sample**

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### Cue condition

The random intercept model did not yield a significant main effect of group for Cue-P3 amplitude ( $z=-0.86$ ,  $p=0.392$ ) or CNV ( $z=1.14$ ,  $p=0.256$ ).

### Go condition

A significant main effect of group emerged for Go-P3 amplitude ( $z=-4.80$ ,  $p<0.001$ ). Post-hoc tests revealed that the preterm group showed significantly reduced Go-P3 amplitude compared to the control ( $t=4.35$ ,  $df=144$ ,  $p<0.001$ ) and ADHD ( $t=2.42$ ,  $df=115$ ,  $p=0.02$ ) groups, with large ( $d=0.79$ ) and moderate ( $d=0.53$ ) effect sizes respectively. The ADHD and control groups do not differ with regard to Go-P3 amplitude ( $t=1.42$ ,  $df=89$ ,  $p=0.156$ ).

### NoGo condition

The random intercept model yielded no significant main effect of group for NoGo-N2 ( $z=1.64$ ,  $p=0.102$ ). No significant main effect of group ( $z=-0.96$ ,  $p=0.337$ ) or recording site (FCz and Cz) ( $z=-2.45$ ,  $p=0.014$ ) emerged for the NoGo-P3. However, a significant group-by-recording site interaction emerged for the NoGo-P3 ( $z=5.52$ ,  $p<0.001$ ). Post-hoc tests revealed that the preterm group showed significantly increased NoGo-P3 amplitude compared to the ADHD group at FCz ( $t=-2.36$ ,  $df=107$ ,  $p=0.020$ ), with moderate-to-large effect size ( $d=0.59$ ), but not at Cz ( $t=0.82$ ,  $df=108$ ,  $p=0.415$ ). In addition, the preterm group demonstrated significantly reduced NoGo-P3 amplitude compared to the control group at Cz ( $t=3.28$ ,  $df=147$ ,  $p=0.001$ ), with moderate effect size ( $d=0.62$ ), but the two groups did not differ significantly at FCz ( $t=-1.86$ ,  $df=130$ ,  $p=0.065$ ). The ADHD group demonstrated significantly reduced NoGo-P3 amplitude compared to the control group at Cz ( $t=2.14$ ,  $df=130$ ,  $p=0.010$ ), with moderate effect size ( $d=0.44$ ), but not at FCz ( $t=0.89$ ,  $df=90$ ,  $p=0.378$ ).